Developing and Validating a Prognostic Model for Mortality in Patients with Heart Failure

Habibullah Muhammad-Kamal

Training courses

Name	Date	Points Achieved
Presentation skills for researchers (all disciplines)	5/12/2019	2
Microsoft Excel: Using as a Database	25/11/2019	2
Microsoft PowerPoint Essentials	23/10/2019	2
Microsoft Word: Creating and Managing Long Documents	21/10/2019	2
Planning Your Research	09/12/2019	1
Structuring Your Thesis	02/12/2019	1
Microsoft PowerPoint: Creating a Research Poster	28/11/2019	1
Researcher Information Skills for Medicine & Health Sciences	26/11/2019	1
UK Data Service Event	29/01/2020	1
Identifying and managing intellectual property issues in research	21/01/2020	1
Writing Scientific Abstracts	15/01/2020	1
Editing Academic Writing	20/01/2020	0.5
Epidemiology	Autumn Term	9
Medical Statistics	Autumn Term	9
Survival analysis	14/5/2020	1
N-trans sandpit 1: Research presentation	06/02/2020	2
N-Trans Workshop 3: Opportunities and skills development in applying for funding	25/06/2020	2
Further presentation skills for researchers	15/02/2020	1

Modules

Name	Term	Pass
Medical Statistics	Autumn Term	Pass with merit
Further Medical Statistics	Spring Term	Pass with merit
Data Organisation and Management in Epidemiology	Spring Term	Pass with Distinction

Abstract

Objectives: Develop and validate a prognostic model for all-cause mortality in patients diagnosed with Heart Failure. Also, to stratify mortality rates of patients diagnosed with Heart Failure, by BMI.

Study design: This was a retrospective open cohort study.

Setting: General practices in England providing data for the Clinical Practice Research Datalink.

Participants: All patients who were 18 years and over at the study start date and had been diagnosed with Heart Failure.

Sample size: The study analysed information on 109,577 patients diagnosed with Heart Failure over a 12-month follow up failure from 1 January 2000 to 31 December 2017 from the Clinical Practice Research Datalink.

Predictors: Predictors considered included age, gender, BMI, NYHA class, systolic blood pressure, prior history of left ventricular hypertrophy, prior history of hypertension, prior history of cerebrovascular disease, prior history of chronic obstructive pulmonary disease, use of diuretics, use of digoxin, use of a calcium-channel blocker, use of lipid-lowering agents, use of an angiotensin-converting enzyme (ACE) inhibitor, use of a β-blocker, creatinine, bilirubin, CRP , prior history of anaemia, , prior history of cardiomyopathy, dyspnoea, prior history of type-2 diabetes mellitus, albumin, race, prior history of coronary heart disease, prior history of cancer , prior history of alcohol use, smoking status, systolic blood pressure, eGFR, , serum albumin, , total cholesterol levels, HDL, LDL, VLDL jugular venous pressure, prior history of pulmonary congestion, prior history of atrial fibrillation, and prior history of chronic kidney disease.

Main outcome measure: 12-month mortality

Statistical analysis: Multivariable cox regression modelling was used to determine predictors of Heart Failure and consequently, develop a 1-year

prognostic model for all-cause mortality in patients with Heart Failure, at any point during the study period.

Results: 93,140 patients did not die during the follow up period and 16,437 died during the follow up period. Out of the 31 predictors assessed 29 were significant. BMI proved to be a significant predictor of heart failure mortality, with the general trend of lower BMI reducing mortality risk. The resulting prognostic model obtained a model validation score (C-statistic) of 0.79. The agreement between the observed and predicted proportion of events showed excellent apparent calibration. The D statistic of 1.65 suggests that the model provides a reasonably high amount of prognostic separation.

Conclusions: Heart failure mortality has several significantly associated comorbidities, drugs, and biomarkers. Lower BMI has been found to generally decrease mortality risk, with an exception being Obesity Class I patients having a lower hazard risk ratio than Pre-Obesity patients. Further research must be completed to better understand the complete system of predictors and confounders responsible for HF mortality.

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I would like to thank my parents and siblings for their support and encouragement during this period.

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1 Introduction

Heart Failure is a condition where the heart does not pump enough blood to meet the needs of the body. This may be due to muscular damage (systolic or diastolic), valvular dysfunction, arrhythmias, or other rare causes. Acute Heart Failure is a common cause of admission to hospital (over 67,000 admissions in England and Wales per year) and is the leading cause of hospital admission in people 65 years or older in the United Kingdom (UK). Prognostic modelling for heart failure mortality is not currently incorporated in clinical practice. As a result, patients with Heart Failure who may be at an increased risk of mortality, are not routinely identified and given prophylactic treatment.

This thesis aims to investigate the risk factors that predispose patients with Heart Failure to mortality with the aim of developing prognostic models to predict this outcome.

This introductory chapter gives an overview of what is already known about the burden of Heart Failure globally and in the United Kingdom (UK). It also describes the risk factors, aetiology as well as current guidelines for management. The need to predict prognosis and gaps in the evidence is highlighted and this is followed by a rationale as well as detailed aims and objectives.

1.1 Definition of Heart Failure

Heart Failure (HF) is a condition in which the heart is unable to generate cardiac output enough to meet the demands of the body without increasing diastolic pressure.[1] Cardiac output itself is defined as the amount of blood the heart pumps in one minute, dependent on heart rate, contractility, preload, and afterload.[2] Diastolic pressure is a measurement of blood pressure that is taken whilst the heart is resting. Diastolic pressure is commonly quoted with systolic blood pressure, which is a measurement of blood pressure that is taken whilst the heart is beating. [3] Symptoms of Heart Failure include breathlessness, ankle swelling and fatigue. This may be in addition to signs such as elevated Jugular Venous Pressure (JVP), pulmonary crackles and peripheral oedema. [4]

Terminology used to describe Heart Failure is based on the measurement of the left ventricular ejection fraction (LVEF). LVEF is the measurement of how much blood is being pumped out of the left ventricle of the heart with each contraction and is expressed as a percentage. Individuals with Heart Failure and an LVEF typically considered as greater than or equal to 50% would be classified as Heart Failure with preserved Ejection Fraction (HFpEF). Patients with an LVEF typically considered as less than 40 % would be considered as Heart Failure with reduced Ejection Fraction (HFrEF). Patients with LVEF in the 40-49% range represent a grey area, which is now defined as Heart Failure with mid-range ejection fraction (HFmrEF)[4]

1.2 Heart Failure Aetiology

There are a wide range of hereditary defects, cardiac conditions and systemic diseases that can result In Heart Failure. Patients with Heart Failure can have a mix of aetiologies which are not mutually exclusive and HF aetiologies vary between high income and low-income countries.

In high income countries, the condition is a result of hypertension, coronary heart disease, valvular disease, or cardiomyopathy. As a result, cardiovascular disease (CVD) risk factors such as tobacco smoking, diabetes, physical inactivity and excess alcohol are largely responsible.[5] This differs from lower income countries who would have aetiologies from conditions such as rheumatic heart

disease, endomyocardial fibrosis, tuberculosis, pericardial disease and anaemia.[6] It is expected that as less economically developed countries industrialise, dominant aetiologies of Heart Failure will shift. This is evidenced in China over the last two decades where the dominant aetiology has shifted from rheumatic heart disease to cardiovascular disease. [7]

There is estimated to be 17 primary aetiologies for Heart Failure however more than two-thirds of all cases of HF can be attributed to ischaemic heart disease, chronic obstructive pulmonary disease, hypertensive heart disease and rheumatic heart disease. [8]

1.2.1 Ischaemic Heart Disease

Ischaemic heart disease is heart disease caused by atheromatous plaques in the coronary arteries that obstruct blood flow leading to ischaemia of the cells of the heart. This weakens the heart's pumping ability and can give rise to acute Heart Failure. [9] Studies such as the Framingham Heart Study have identified risk factors for coronary heart disease to include hypertension, diabetes, hyperlipidaemia, and smoking. As the increased recognition and treatment of these cardiovascular risk factors have increased, death rates from cardiovascular causes have steadily declined since the 1960s. [10] Incidence of ischaemic heart disease, hypertension, diabetes and other chronic diseases parallel the increased consumption of food high in fat, sugar and sedentary behaviour, and unless preventative health strategies are implemented the incidence and prevalence of these diseases will continue to increase. [11]

Ischaemic Heart Disease accounted for 15.7% of all age-standardised deaths globally in 2013. [12]Between 1990 and 2010 it is known that the prevalence of ischaemic HF increased from 240 to 270 per 100,000 person years for men and remained stable at 190 per 100,000 person-years in women. Age-standardised rates of myocardial infarction have decreased between 1990 and 2010 in Australasia, Europe, and North America between 1990 and 2010 in general, however there has been an increase in the number of myocardial infarctions in Eastern Europe. The incidence of acute myocardial infarction worldwide is highest in Eastern Europe and Central Asia with more than 340 cases per

100,000 person years for men and 180 cases per 100,000 person years for women. The lowest rates of acute myocardial infarction were observed in the high-income countries in Asia. [13]

The Olmstead County cohort reported that between 2000 and 2010 in Oklahoma, the proportion of ischaemic HFpEF increased from 29.0% to 32.6% whilst the proportion of ischaemic HFrEF declined from 39.8% to 29.4%. [14] The decrease in proportion of patients with HFrEF is due to a reduction in myocardial infarction through primary and secondary prevention. [15]

1.2.2 Hypertensive Heart Disease

Hypertensive Heart Disease results from cardiac myocytes being exposed to elevated mechanical stress and neurohormones during an increase in blood pressure and this increases myocardial mass and results in left ventricular hypertrophy. These changes can progress to HFpEF or HFrEF even without myocardial infarction and obstructive epicardial coronary arteries. [16] In the Olmsted Cohort 89.3 % of patients with HFpEF had hypertension and 73.6% of patients with HFrEF had hypertension [17] Lifetime risk of HF for individuals with blood pressure greater than 160/90 mmHg is double that of those with blood pressure less than 140/90 mmHg. [18] Randomised controlled trials have reported that effective treatment of moderate and severe hypertension reduces the risk of HF by 87%.[11] In the United States of America, antihypertensive treatment has reduced the incidence of HF by 50%. [19]

1.2.3 Valvular Heart Failure

Valvular Heart Failure secondary to rheumatic heart disease is the greatest burden of valvular disease. Cases of valvular heart disease are degenerative in nature in developed countries and incidence is also low. In the USA, the prevalence of valve disease diagnosed by echocardiography is 2.5% and increases with age. The prevalence of clinically diagnosed valvular disease is 1.8%. In developed nations the incidence of rheumatic fever is less than one case per 100,000 person-years.[20]This is attributed to improved living conditions and availability of antibiotic therapy.

In developing countries however, valvular HF resulting from rheumatic disease contributes substantially to morbidity and mortality. Over 15.6 million people have rheumatic heart disease globally with 470,000 new cases and 233,000 deaths per year. [21] Sudan, for example, has more than 100 cases per 100,000 person-years. [22] Like its aetiology, the epidemiology of Heart Failure, as a disease, is complex.

1.3 Epidemiology of Heart Failure

1.3.1 Prevalence

Worldwide prevalence of Heart Failure has been increasing over the past decade, with higher rates reported in men compared to women.[24] This trend has been echoed in a study by Curtis et al which showed that HF prevalence increased from 90 to 121 per 1000 people between 1994 and 2003. It is important to note that this could have been because of increasing awareness and diagnosis of HF, an ageing population, or an improvement in cardiovascular disease management. The UK follows the worldwide trend as Heart Failure prevalence has increased in absolute terms between 2002 and 2014 (from 750 127 to 920 616; 23%) but has remained relatively stable once standardised by age and sex (1.5% to 1.6%). This is reportedly due to an increase in population size and age. The study also reported that prevalence was higher in men than in women (1·8% in men vs 1·2% in women; adjusted rate ratio (RR) 1·52, 95% CI 1.51–1·53).[25] An analysis of HF prevalence in Spain also showed a steady increase from 895 per 100,000 population per year in 2000 to 2126 cases per 100,000 per year in 2007. This study also showed higher rates in men compared to women. [26]

Across the world, age is reported to increase prevalence of HF. A study conducted in Portugal reported a Heart Failure prevalence of 1.36% in the 25–49-year-old group, 2.93% in the 50–59 year-old group, 7.63% in the 60-69 year old group, 12.67% in the 70-79 year old group and 16.14% in patients older than 80 years old.[27] A German study which established the prevalence of HF in Germany as 1.6% in women and 1.8% in men[28] – also showed an increase in prevalence with age. The Swedish prevalence of HF is described as 1.8%, before

adjustment for demographic composition, but 2.2% after.[29] HF prevalence in Italy is stated at 1.44%, with rates also increasing with age.[30]

Heart Failure in Asian countries is reported to be much higher than those in Europe and North America. In China, whilst the Heart Failure prevalence is estimated at 1.3% this roughly equates to 4.2 million people suffering from the condition because of China's population size.[31] One million people in Japan also have the condition, which accounts for 1% of the population[32] and India has a prevalence estimated between 0.12 and 0.44, which is known to be underestimated.[33] Malaysia and Singapore have prevalence of 6.7% and 4.5% respectively. [34 35]

South America is estimated to have a HF prevalence of around 1% whilst the Australian prevalence is reported to be between 1-2%. [36 37] Whilst aetiologies and clinical characteristics have been studied in Africa, there are no population studies to provide insight into prevalence or incidence. [38]

It is also important to be aware that the worldwide trend of an increase in Heart Failure precedence has its exceptions. Canada, in contrast to this trend, has had a decreasing prevalence between 1994 and 2004 from 20.3 to 18.4 per 100,000 people.[39]

1.3.2 Incidence

Whilst prevalence is an important epidemiological metric to measure the frequency of Heart Failure across the world, incidence can provide us with important information on the number of new cases in different populations.

Over 900,000 people in the UK live with definite or probable Heart Failure and 68,000 people develop the condition per year.[40] Heart Failure affects 10 million people across Europe and in 2004 there were a total of 1.3 million new cases of Heart Failure in Europe.[41]

There is evidence to suggest that there is a higher incidence of Heart Failure in men compared to women both in the USA and the UK. There is also evidence to suggest incidence increases with age. The Framingham study in the US

reported that for those aged 50-59 years old, incidence was 0.3% per annum in men and 0.2% per annum in women. This rose to 2.7% per annum in men and 2.2% in women aged 80 to 89 years old. [42] In the UK, the Hillingdon study reported an incidence rate of 0.2% per annum in men and a 0.1% per annum in women for those aged 55 to 64 years old. For those aged 85 and over this rose to 1.7% in men and 1% in women. [43] The Framingham study showed a significantly higher incidence of the condition in men with an age standardised incidence ratio of 1.67, whilst the Hillingdon study also found a significantly higher incidence of the condition in men with an age standardised ratio of 1.75.[42 43]

There is no data available on changes over time in the Hillingdon study as it was cross-sectional in design however it did show that Heart Failure incidence differs between different age groups (Figure 2).[43] A study conducted by Conrad et al showed that between 2002 and 2014, Heart Failure incidence standardised by age and sex increased by 7% whilst the absolute number of newly diagnosed Heart Failure in the UK increased by 12%.[25] This is unlike the Framingham study which reported a 7% non-significant decrease in age adjusted Heart Failure incidence in men and a correspondingly significant decrease in women, from 1950 to 1999.[42]

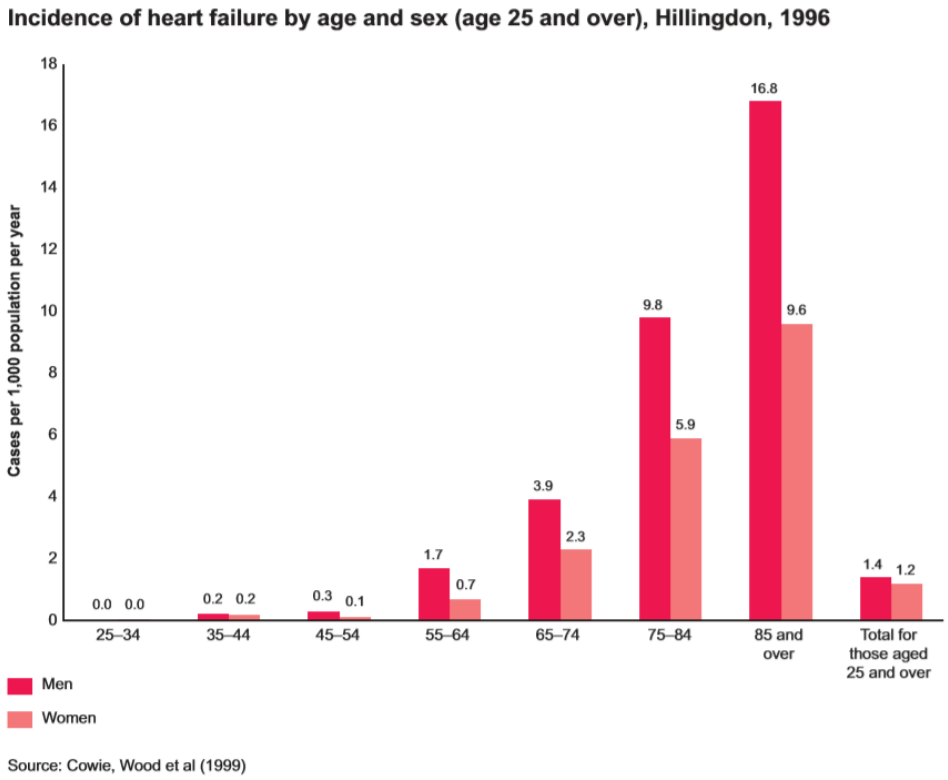


Figure 1- Incidence of Heart Failure by age and sex (25 and over), Hillingdon 1996 [43]

Other than the studies stated above, data on Heart Failure incidence remain sparse.

1.3.3 Outcomes

There were 9140 deaths attributed to Heart Failure in 2005 in England and Wales.[44] This is widely acknowledged to be an underestimate due to guidance given on death certificates that indicate that Heart Failure is not a cause of death but a mode of death. As a result, doctors do not record Heart Failure as underlying cause of death. According to a study conducted by Sutcliffe et al, Heart Failure mortality in the UK had risen from the 1950's to the 1970's before declining between the 1970's to 1990's – and then levelling off from the 1990's till today (Figure 2). [45]

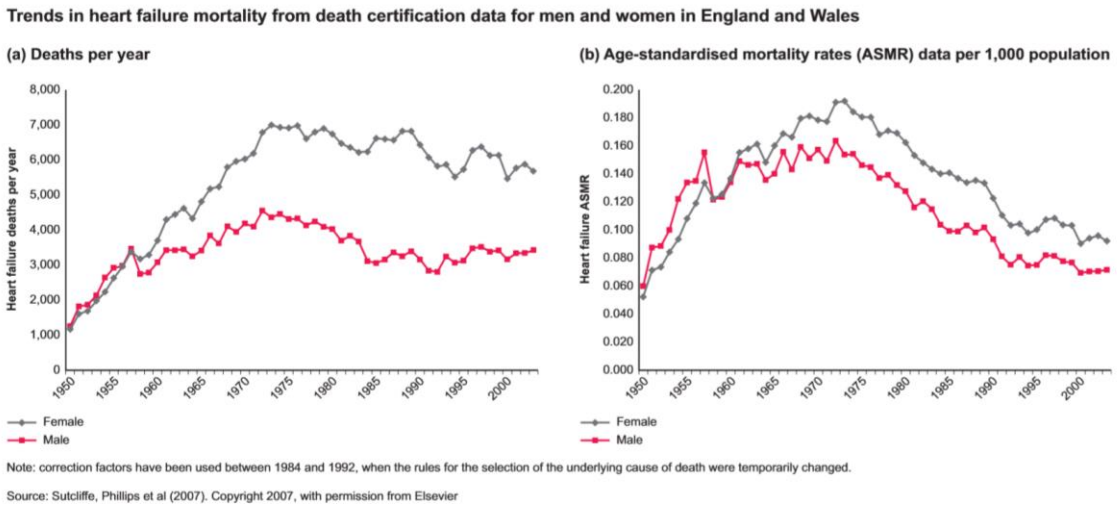


Figure 2- Trends in Heart Failure mortality for men and women in England and Wales[26]

Prognosis of Heart Failure in the UK remains poor although improved by recent advances in treatment. One-year survival rates are better for patients with breast, prostate and colon cancer compared to Heart Failure sufferers (Figure 3). [46] [43] There is known to be a high risk of mortality in the first month after diagnosis of Heart Failure [42] [43] A study by Mehta et al in South East England showed that between the two periods where two cohort studies were completed (Hillingdon-Bromley and Hillingdon-Hastings), there was an improvement in survival that was independent of demographic differences and severity of symptoms and diagnosis. [47]

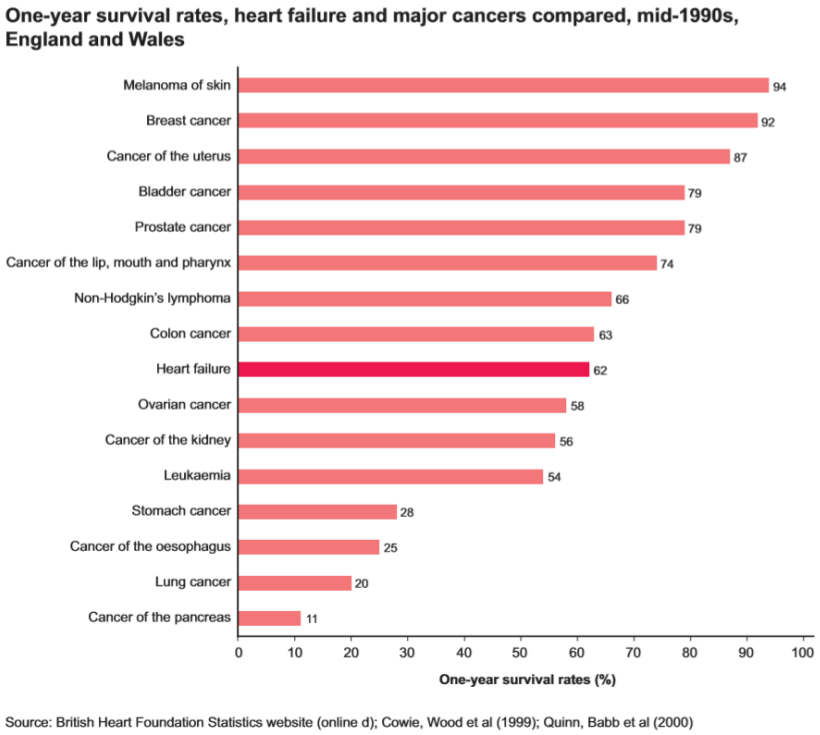


Figure 3: One-year survival rates, Heart Failure and major cancers compared, mid-1990s, England and Wales.[46] [43]

HF outcomes have been extensively investigated in the USA. In the USA, one in 8 deaths have HF mentioned on the death certificate, 20 % of which have HF as the primary cause of death.[48] The Organised Program to Initiate lifesaving Treatment in Hospitalised Patients with Heart Failure (Optimize-HF) study found significantly higher in-hospital mortality with patients with HFrEF (3.9%) compared with HFpEF (2.95%). [49] Another study by Cheng et al discovered that there was a higher risk of readmission after one year in HFrEF and HFmrEF compared to HFpEF.[50]

In Europe there is reportedly a higher 90-day mortality in patients with HFrEF (12%) compared to HFpEF (10%). Hospital mortality is predicted to be 6.4%.[51] [52] 1-year mortality is estimated to be at 23.6% for acute HF and 6.4% for chronic HF.[53]

In China, 30-day mortality is 5.3% whilst in Taiwan it is 3.9%.[54] A study in Singapore followed a cohort of 15,774 HF patients from 1991 to 1998, calculating total mortality at 2.5% [55] A Korean analysis of patients with HFrEF

showed 3.8% mortality at 60 days and 9.2% at one year whilst hospitalisation rates were 3.1% at 60 days and 9.8% at the year.[56] In Japan, there is reportedly an 8.9% 1 year mortality rate in HFrEF compared to 11.6% in HFpEF[57]. In Australia, a 1-year mortality of 20.5-20.7% has been estimated in HF patients.[58]

1.4 International and National Burden of Heart Failure

1.4.1 Financial Burden

Heart Failure is increasing in prevalence worldwide and affects at least 26 million people across the globe.[59] Heart Failure costs the National Health Service (NHS) £629 million as of the year 2000, with hospital inpatient care representing the major expense (Figure 4). Other expenses include primary care, hospital day-case care, hospital outpatient care, outpatient investigations and drugs.[60] In the United States of America (USA), as of 2012, Heart Failure cost about $30.7 Billion dollars where 68% was attributable to direct medical costs. Expenditure by healthcare systems on the disease are considerable and are expected to increase in ageing populations. In the USA, projections show that by 2030, costs will increase by 127%. [61]

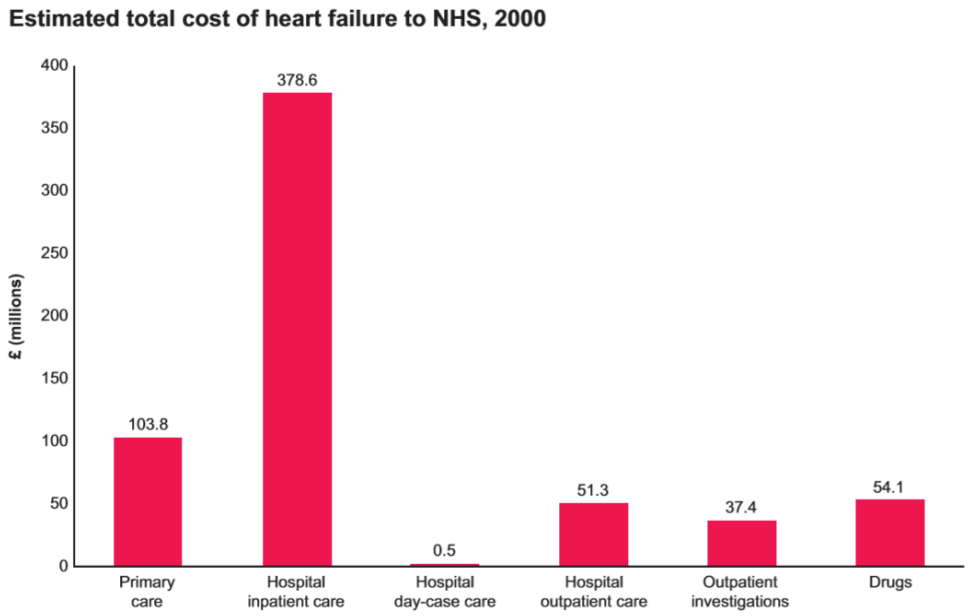


Figure 4: Costs of Heart Failure to the NHS (Year 2000)[40]

1.4.2 Hospitalisations

In hospitalized elderly patients aged >65 in high income countries, Heart Failure is the most common diagnosis.[62] HF also represents between 1-2% of all hospital admissions. [63] In the UK, 5% of all admissions from the emergency department to the hospital are for HF and HF hospitalisations are expected to increase by 50% by 2035.[64] The age standardised hospitalisation rate in France was 246.2 per 100,000 population in 2012. [65] In the Netherlands, Scotland and Sweden, hospital admissions for HF have declined after peaking in the 1990's. In Europe generally, rates of hospitalisation have been stable between 2000 and 2010, whereas standardised inpatient mortality has decreased by 3.3% per year. [65]

In the USA, HF leads primary diagnosis for hospitalisation and has approximately 1 million discharges every year between 2000 and 2010.[66] Between 1979 and 2004, the proportion of hospitalisations resulting from Heart Failure increased by 300%. This occurred during a period where age adjusted hospitalisation rates for HF increased from 219 to 390 per 100,000 person years.[67] It has also been described in the US that African American individuals have a 50% higher likelihood of hospitalisation, 20% higher for Hispanic individuals and 50% lower for Asian individuals compared to white individuals. [68] This data highlights the significance of ethnicity as a potential risk factor for hospitalisation for Heart Failure, however research exists that also describe the health-related risk factors for HF.

1.5 Risk Factors associated with Heart Failure incidence and mortality

1.5.1 Ischaemic Heart Disease

Ischemic Heart Disease describes a range of conditions that arise when the arteries of the heart cannot provide enough oxygen rich blood to the heart itself. This is due to the build-up of plaque in the coronary arteries that can either partially or completely block the artery.[69]

Ischemic Heart Disease is a well-known risk factor for Heart Failure.[70] More than one-third of patients develop HF in seven to eight years after a myocardial

infarction (MI), especially those patients with left ventricular dysfunction.[71] MI history also increases the lifetime risk of Heart Failure in both men and women. [72] In the OPTIMIZE-HF registry 15% of patients with ischaemia as a primary cause of hospitalisation also had HF. These patients also had worse 60- and 90-day mortality as well as hospital mortality. Despite this, there is conflicting evidence on how better management of MI impacts HF trends. This is because successful MI treatment can result in a greater population of patients at risk of Heart Failure whilst the incidence of post MI HF might decrease if MI severity decreases.[73]

An analysis of the Framingham Heart Study by Velagaleti et al found that whilst the 30-day incidence of HF after MI rose from 10% to 23.1%, the 30-day mortality after MI declined from 12.1% to 4.1%.[74] These trends were also seen after 5 years which showed an increase from 27.6% to 31.9% for incident HF and a decrease from 41.1% to 17.3% for mortality respectively.[74] These results contrast evidence from Chen et al which showed that between 1979 and 1994, where 36% of participants with incident MI developed HF, the incidence of HF declined by 2% every year in Olmsted within a cohort of patients with MI. [75]

1.5.2 Hypertension

Hypertension is high blood pressure. Classification of high blood pressure can differ from individual to individual however in general, high blood pressure is 140/90mmHg or more. [76] Risk of Heart Failure associated with hypertension is smaller than that associated with ischemic heart disease, however due to its greater prevalence it contributes more to the population burden. An example of this is in the Framingham study where 75% of incident HF cases had antecedent Hypertension. [77]

There is evidence to suggest that Hypertension was more of a contributing factor for HF in women than men. For example, women had a threefold increase in risk of developing HF whilst men had a two-fold increase and the population attributable risk of HF imparted by Hypertension was estimated to be 39% in men and 59% in women.[78] The Rotterdam study also echo these findings, reporting that Hypertensive women were 2.6 times more likely to

develop HF than non-hypertensive women. This is in compared to men in the same study who were at no higher risk regardless of their blood pressure status.[78]

The Framingham Heart Study reports that the more severe an elevation in blood pressure the greater the risk of developing Heart Failure. The Lifetime risk for individuals with blood pressure greater than or equal to 160/90 mmHg is double that of those with blood pressure less than 140/90 mmHg. [18] In addition to this, having both Hypertension and Heart Failure is associated with an increase in 5-year mortality after the onset of hypertensive Heart Failure in men and women (76% and 69% respectively). [20] There is evidence that suggest hypertensive treatment can reduce incidence of Heart Failure by almost 50%.[79]

1.5.3 Diabetes

Recent research shows that diabetes and insulin resistance are linked to HF development, with diabetes increasing the risk of Heart Failure by twofold in men and five-fold in women. [80] [81] The Heart and Oestrogen/progestin Replacement Study (HERS) corroborated this research by concluding that, in a cohort of post-menopausal women with a history of heart disease, women with diabetes and an elevated BMI or renal insufficiency were at higher risk of Heart Failure. This is because they had incidence rates of HF of 7% and 13% respectively - which was significantly greater than that of women without diabetes which was 0.4%. Hyperglycaemia (defined as a fasting blood glucose >300mg/dL) increased the hazard threefold. [82]

According to the Olmstead Cohort, the prevalence of diabetes increased 3.8% every year in patients with HF from 1979 to 1999. This increase was pronounced in older individuals (those aged >75) who had a fourfold increase in the odds of having diabetes with HF. HF survival is worse in the presence of diabetes – with 5-year survival of 46% in patients with only Heart Failure but 37% in patients with diabetes and Heart Failure.[83]

1.5.4 Dyslipidaemia

Elevated cholesterol levels are a well-known risk factor for heart disease and are therefore also linked to Heart Failure development. It is important to note however that it is the increased ratio of total cholesterol to HDL cholesterol that is associated to HF risk and not elevated levels of total cholesterol alone. [83] [80] There is evidence to suggest that lowering cholesterol can prevent HF, as statin treatment in patients with coronary artery disease reduced HF incidence and decreased all-cause mortality in patients who developed HF in an analysis of the Scandinavian simvastatin study. [85]

1.5.5 Smoking

Tobacco is the single largest preventable cause of disease and premature death in the USA. Current smokers have higher risks for the development of Heart Failure compared to ex-smokers and non-smokers. The Coronary Artery Surgery Study (CASS) showed that smoking was independently associated with 47% increased risk of developing Heart Failure. [86]

1.5.6 Other Risk Factors

There is evidence to suggest that HF with preserved LVEF and HF with reduced LVEF have different risk factors. Independent predictors of the onset of HF and preserved LVEF include elevated systolic blood pressure, atrial fibrillation, female sex. Previous myocardial infarction and left bundle branch block morphology are reported to have reduced odds of HF and LVEF. [87]

Obesity also increases the risk of Heart Failure, with estimates suggesting that a BMI greater than 30 can double the risk of Heart Failure. [88] Once Heart Failure is established however, there is evidence to suggest that obesity is associated with improved outcomes. [89] An analysis of 8,000 patients in the Digitalis Investigation Group Trial showed that obese patients had a 19% lower risk of death than individuals of normal weight.

Renal failure is also reported as a risk factor, with early kidney disease reported to increase the odds of incident HF by 80%. [90] kidney disease is also known as a strong predictor of mortality amongst those with HF, however the use of

angiotensin-converting-enzyme (ACE) inhibitors seemed to attenuate this increased risk. [82]

There are also other proposed factors such as psychological stress, socioeconomic status that are known to increase risk. A variety of biomarkers, morphological parameters, and genetic factors such as natriuretic peptide, troponin, genetic mutations, left ventricular size and mass are known to be associated with HF.[91]

These conditions are not only known to increase the risk for developing HF, but also contribute to morbidity and mortality for patients with established Heart Failure. [92] Risk of preventable hospitalizations and mortality is reported to strongly increase with the number of comorbid conditions, and therefore prognostic modelling is important. [93] Prognostic modelling is also of value when it comes to the diagnosis and management of Heart Failure.

1.6 Current Guidelines for Diagnosis and Management of Heart Failure

1.6.1 Acute Heart Failure

Acute Heart Failure refers to rapid onset or worsening of symptoms of Heart Failure. It is a life-threatening medical condition requiring urgent evaluation and treatment, typically leading to urgent hospital admission for diagnosis and management.[4]

1.6.1.1 Diagnosis of Acute Heart Failure

The National Institute for Health and Care Excellence (NICE) have recommended that for diagnosis of acute Heart Failure, people with suspected Heart Failure after a detailed history and examination should have a single measurement of serum natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NT-proBNP]. To rule out Heart Failure, patients must have less than 100 nanograms per litre for BNP and 300 nanograms per litre for NT-proBNP. [94] Once patients are confirmed to have raised natriuretic peptide levels, a transthoracic Doppler 2D echocardiography is recommended to be performed to establish the presence or absence of cardiac abnormalities. This is advised to be done within 48 hours of admission

to guide early specialist management. Pulmonary artery catheterisation is not recommended to be routinely offered. [95] Acute Heart Failure once diagnosed, should proceed to be managed in the hospital.

1.6.1.2 Management of Acute Heart Failure

For patients diagnosed with acute Heart Failure, treatment depends on many factors.

An early stage, mechanical circulatory support should be offered to patients with potentially reversible severe acute Heart Failure or patients who are potential candidates for transplantation. [95]

Intravenous diuretic therapy is recommended to be routinely offered after diagnosis of acute Heart Failure with either a bolus or infusion strategy. For patients who are already prescribed diuretics, they should be increased in dose. The patient should be consulted on the best strategies for the expected increases in urine output as renal function, weight and urine output are closely monitored after prescription.[96] In a situation where a patient has concomitant myocardial ischaemia, severe hypertension or regurgitant aortic or mitral valve disease and requires intravenous nitrates, blood pressure should be closely monitored in a setting where level 2 care can be provided. [97] Level 2 care refers to a level of care between intensive therapy and general hospital wards. Examples refer to patients who no longer need intensive therapy but require step down care or patients admitted from wards, Accident and Emergency or theatres to prevent them requiring intensive therapy (east of England critical care operational delivery network). Whilst inotropes and vasopressors should not be routinely prescribed for people with acute Heart Failure, they should be considered in Heart Failure patients with reversible cardiogenic shock. [98] These treatments should also be administered in a setting where level 2 care can be provided or a cardiac care unit or high dependency unit. Sodium nitroprusside should not be offered to Heart Failure patients. [95]

If a patient diagnosed with acute Heart Failure also has cardiogenic pulmonary oedema, it is not recommended for non-invasive ventilation to be used. Non-

invasive ventilation is indicated without delay at acute presentation or as an adjunct to medical therapy when cardiogenic pulmonary oedema presents with severe dyspnoea or acidaemia. It is also indicated as an adjunct to medical therapy if the patient's condition has failed to respond. [99] Patients who, despite treatment, are leading to or complicated with respiratory failure or reduced consciousness or physical exhaustion should be considered for invasive ventilation. Whilst ultrafiltration should not be offered routinely for patients with Heart Failure, it is recommended for people with confirmed diuretic resistance. [95]

Patients are expected to have stabilised for 48 hours before being discharged or resumed on beta-blockers. If a person diagnosed with Heart Failure is currently taking beta-blockers, it is recommended that they continue the beta blocker treatment once stabilised unless they have a heart rate less than 50 beats per minute, shock or second- or third-degree atrioventricular block. Beta-blocker treatment should also be started or restarted during hospital admission for patients diagnosed with Heart Failure with left ventricular systolic dysfunction once stabilised. [100] Patients who are diagnosed with a reduced left ventricular ejection fraction in addition to acute Heart Failure are to be offered an angiotensin-converting enzyme (ACE) inhibitor. [101] If this is poorly tolerated or leads to intolerable side effects, an aldosterone antagonist should be offered.[102] It should be noted that patients treated with beta-blockers, ACE inhibitors or aldosterone antagonists should have their renal function, electrolytes, heart rate, blood pressure, and overall clinical status measured during treatment. [95]

Patients with Heart Failure due to severe aortic stenosis assessed suitable for surgery should be offered aortic valve replacement. Patients with Heart Failure due to severe mitral regurgitation assessed suitable for surgery should be considered for surgical mitral valve replacement. If patients are assessed as unsuitable for aortic valve replacement, a transcatheter aortic valve implantation should be considered. [95]

Recommendations for both the diagnosis and management of acute Heart Failure is detailed on Figure 4.

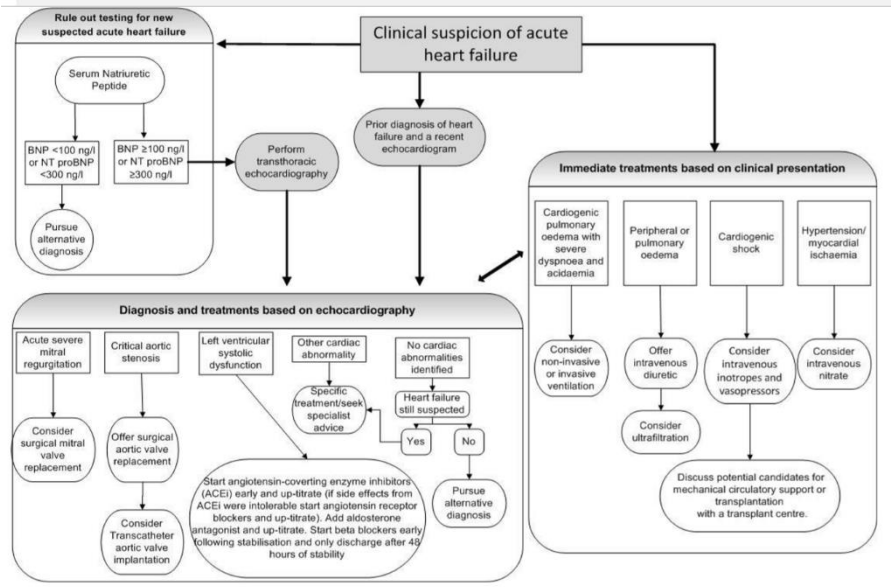


Figure 4- Diagnostic and treatment algorithm for clinical suspicion of acute Heart Failure [95]

1.6.2 Chronic Heart Failure

Chronic Heart Failure refers to patients who have been diagnosed with Heart Failure for a long period of time. A treated patient with symptoms and signed that have remained unchanged for a month are described as having chronic stable Heart Failure. If a chronic stable Heart Failure patient deteriorates, they are described as 'decompensated', and this can happen suddenly or slowly and can lead to hospitalisation.[4] Diagnosis of chronic Heart Failure differs distinctly from that of acute Heart Failure.

1.6.2.1 Diagnosis of Chronic Heart Failure

Like acute Heart Failure, diagnosis of chronic Heart Failure requires the measurement of NT-proBNP after a detailed history and clinical examination.

An NT-proBNP level above 2000 nanograms per litre is recommended to have specialist assessment and transthoracic echocardiography within two weeks. For patients who have an NT-proBNP level between 400 and 2000 nanogram per litre, they are recommended to have specialist assessment and transthoracic echocardiography within 6 weeks. A diagnosis of Heart Failure is unlikely in patients who have an NT-proBNP level below 400 nanograms per litre. With these patients, alternative causes of Heart Failure must be reviewed. [104]

It is important to be aware that serum natriuretic peptide levels are lower in patients with obesity. [105] Likewise, serum natriuretic peptide levels are higher in patients who are older than 50 years of age; diagnosed with left ventricular hypertrophy, tachycardia, ischaemia, right ventricular overload, hypoxaemia (including pulmonary embolism), renal dysfunction (eGFR less than 60ml/min/1.73m^2), sepsis, chronic obstructive pulmonary disease, diabetes, or cirrhosis of the liver.[105]

The level of serum natriuretic peptide does not distinguish between Heart Failure with reduced ejection fraction and Heart Failure with preserved ejection fraction. This can be distinguished through echocardiography, which can also be used to exclude important valve disease and detect intracardiac shunts. If imaging with the transthoracic echocardiogram is poor, radionuclide angiography, cardiac MRI and transoesophageal echocardiography could be used alternatively. [106]

To exclude similar disorders that may present in a similar manner or evaluate aggravating factors, extra investigations such as the ECG, chest X-ray, urinalysis and peak flow spirometry are recommended to be undertaken. Blood tests providing renal function profile, thyroid function profile, liver function profile, lipid profile, glycosylated haemoglobin and full blood count are also deemed to be clinically useful. Once Heart Failure has been confirmed then steps must be taken to assess severity, aetiology, precipitating factors, type of cardiac dysfunction and correctable causes. If diagnosis of Heart Failure remains

suspected and the underlying cardiac abnormality is not confirmed, the patient must undergo further investigation before management.[103]

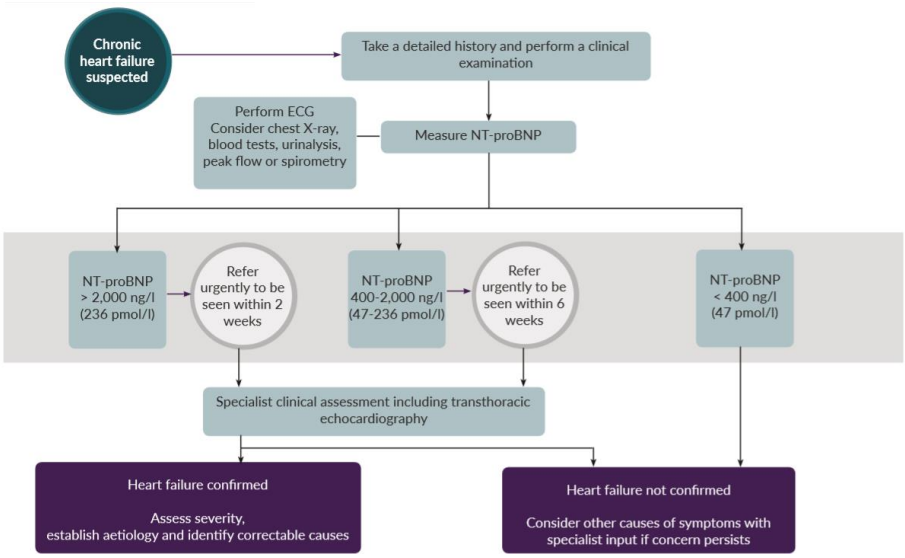


Figure 5- Diagnostic algorithm for clinical suspicion of chronic Heart Failure (NICE)

1.6.2.2 Management of Chronic Heart Failure

1.6.2.2.1 Management of All Chronic Heart Failure

With regards to pharmacological treatment, diuretics are recommended for patients diagnosed with chronic Heart Failure. This is used to relief congestive symptoms and fluid retention common with these patients and must be titrated up or down according to need. For patients with preserved ejection fraction, the diuretic of choice is usually a loop diuretic at a medium to low dose. [107]

Care must be taken when prescribing certain drugs to patients with Heart Failure. Calcium channel blockers such as verapamil, diltiazem and short acting dihydropyridine agents are to be avoided with patients with reduced ejection fraction.[109] The decision to prescribe amiodarone must be done with a specialist and must be reviewed at a 6-monthly clinical review in addition to liver and thyroid function tests. [103] Anticoagulation therapies must be considered for patients with a history of thromboembolism, left ventricular

aneurysm or intracardiac thrombus - but only if they are in sinus rhythm. [110] Contraception and pregnancy should be discussed with patients of childbearing age with Heart Failure and specialty care should be shared between a cardiologist and an obstetrician for pregnant patients. [103]

Patients with Heart Failure are recommended to have a personalised exercise based cardiac rehabilitation programme. [110] Such a programme should have components such as an assessment for suitability, an easily accessible format and setting and a psychological and physical component. This may be incorporated into an existing programme of cardiac rehabilitation. [111]

Patients with Heart Failure are recommended to be vaccinated against pneumococcal disease and influenza. [112] Intake for these patients should also be reduced for both salt and fluids if they are found to be high. Salt substitute containing potassium should be avoided. [113] Likewise, if they have dilutional hyponatremia, they should also restrict fluids. [114] These restrictions should be continuously reviewed. [103]

An important part of Heart Failure management is monitoring. This monitoring should include a clinical assessment of functional capacity, fluid status, cardiac rhythm, cognitive status, and nutritional status. This is in addition to a review of medication and an assessment of renal function. More detailed review would be needed if the patient has significant co-morbidity or if their condition has deteriorated since the previous review. Frequency and monitoring of an individual will depend on their status and stability. If medication has changed, the monitoring interval is expected to be short but at least every six months for stable patients with Heart Failure. [115]

1.6.2.2.2 Management of Chronic Heart Failure with Reduced Ejection Fraction

The first line of treatment recommended for patients with chronic Heart Failure with reduced ejection fraction is an ACE inhibitor licenced for Heart Failure in conjunction with a beta-blocker licenced for Heart Failure. [103] [116]

ACE inhibitor therapy should begin at a low dose and be titrated upwards at short intervals until the target or maximum tolerated dose is reached. [116] After each dose increment, blood pressure should be measured – as well as renal function, serum sodium and potassium. Serum sodium, potassium and renal function should also be measured before as well as one to two weeks after starting the ACE inhibitor. Once the maximum tolerated or target dose of ACE inhibitor is reached, treatment should be monitored monthly for three months, then at least every six months or when the patient becomes acutely unwell. [103] [116]

Angiotensin receptor blockers (ARBs) licensed for Heart Failure are recommended as an alternative to ACE Inhibitors for patients with chronic Heart Failure with reduced ejection fraction unable to tolerate the side effects of ACE inhibitors. [103]Like ACE inhibitors, blood pressure should be measured after each dose increment – as well as renal function, serum sodium and potassium. Serum sodium, potassium and renal function should also be measured before as well as one to two weeks after starting the ARB. Once the maximum tolerated or target dose of ARB inhibitor is reached, treatment should be monitored monthly for three months, then at least every six months or when the patient becomes acutely unwell. [103] [117]

If both ARBs and ACE inhibitors are not well tolerated, then hydralazine in conjunction with nitrates should be considered for people who have Heart Failure with reduced ejection fraction. [117]

Patients who are stable and already taking beta-blockers for a co-morbidity before developing Heart Failure with reduced ejection fraction are advised to switch to a beta-blocker licensed for Heart Failure. These beta blockers are recommended to be taken in a ‘start low, go slow’ manner, with heart rate and clinical status assessed after each titration. Blood pressure should also be measured after each dose increment. The presence of peripheral vascular disease, erectile dysfunction, diabetes, interstitial pulmonary disease, chronic obstructive pulmonary disease does not constitute valid reasons to withhold a beta-blocker and neither does age. [103]

Mineralocorticoid receptor antagonists (MRAs) should be provided in addition to ACE inhibitors and beta-blockers to patients with Heart Failure with reduced ejection fraction if they continue to have symptoms of Heart Failure. Blood pressure should be measured after each dose increment – as well as renal function, serum sodium and potassium. Once the maximum tolerated or target dose of the MRA is reached, treatment should be monitored monthly for three months, then at least every six months or when the patient becomes acutely unwell. [103]

Another option for patients with chronic Heart Failure with a reduced ejection fraction considered symptomatic would be Sacubitril/Valsartan. This is recommended if the patient is already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or ARBs and has New York Heart Association (NYHA) class II to IV symptoms and a left ventricular ejection fraction of 35% or less. [118]

For patients who may have stable Heart Failure with systolic dysfunction, ivabradine is recommended as a potential treatment. This should be initiated by a Heart Failure specialist with access to a multidisciplinary Heart Failure team. Conditions for its use include that the patient has a New York Heart Association (NYHA) classification of II to IV (A functional classification system that categorises Heart Failure patients based on their level of impairment of physical activity), in sinus rhythm with a heart rate of 75 beats per minute or more and a left ventricular ejection fraction of 35% or less. It is also expected that ivabradine is given in combination with standard therapy including ACE inhibitors, beta-blockers, aldosterone antagonists or given when beta blocker therapy is contraindicated or not tolerated. This is expected to be after a four-week stabilisation period. [119]

For patients who are of African or Caribbean origin with moderate to severe Heart Failure (NYHA Class III/IV) with a reduced ejection fraction may be treated with hydralazine with nitrate. [120]

Digoxin is also recommended for worsening or severe Heart Failure with reduced ejection fraction despite first line treatment. [121]

Patients with chronic Heart Failure, reduced ejection fraction and chronic kidney disease, response to titration of medicines must be closely monitored due to increased risk of hypokalaemia. [122] An eGFR of less than 45ml/min/1.73m^2 would normally require lower doses of ACE inhibitors, ARBs, MRAs, and digoxin. A renal physician should be considered for consultation for patients with an eGFR less than 30ml/min/1.73m^2. For patients under 75 years old with chronic Heart Failure with reduced ejection fraction and an eGFR above 60 ml/min/1.73 m2, measured NT-proBNP should be considered as part of a treatment optimisation protocol. [103]

Interventional procedures may sometimes be required to manage a deteriorating patient. Heart Failure patients with severe refractory symptoms or refractory cardiogenic shock should be considered for specialist referral for cardiac transplantation. [123] Coronary revascularisation, however, should not be offered to Heart Failure patients with reduced ejection fraction and coronary heart disease. This is according to NICE; however, the European Society of Cardiology recommend the treatment if the patients' clinical condition permits. [103] [124] Implantable cardioverter defibrillators (ICDs), cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) are recommended as treatment options for people with Heart Failure. The choice of treatment can depend on many factors, including NYHA class, length of QRS complex and presence of LBBB (as shown in Figure 7). Implantable cardioverter defibrillators are also recommended for patients with previous serious ventricular arrythmia. This refers to patients who, without a treatable cause, have survived cardiac arrest caused by tachycardia, ventricular fibrillation, spontaneous sustained VT causing syncope or significant haemodynamic compromise. Patients who have sustained VT without syncope or cardiac arrest and have an LVEF less than 35% with a NYHA classification of III or IV would also be recommended to have an ICD. [124] [103]

The benefits and harms of a cardioverter defibrillator remaining active in a person should be reviewed at each monthly review of Heart Failure, whenever care goals change or as part of advanced care planning if it is thought that the patient is nearing the end of life. [103]

If the patient is nearing end of life, it is important to discuss their palliative care needs with a specialist Heart Failure multidisciplinary team and consider a needs assessment for palliative care. Prognostic tools should not be used to refer a person with Heart Failure to palliative care services. Unless the patient has comorbidities such as chronic obstructive pulmonary disease, they should not be offered long term oxygen therapy for advanced Heart Failure. [103]

Recommendations for the management of chronic Heart Failure is detailed in Figure 6.

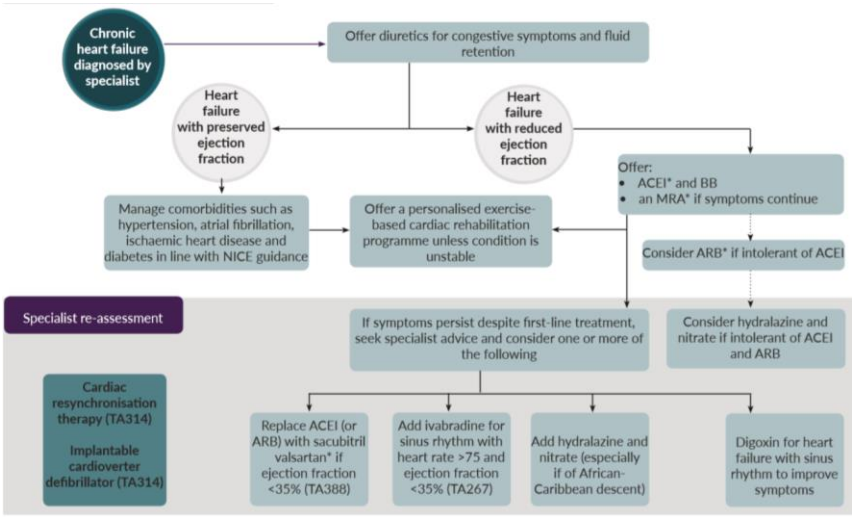


Figure 6- Management algorithm for chronic Heart Failure [103]

	NYHA class			
QRS interval	I	II	III	IV
<120 milliseconds	ICD if there is a high risk of sudden cardiac death			ICD and CRT not clinically indicated
120–149 milliseconds without LBBB	ICD	ICD	ICD	CRT-P
120–149 milliseconds with LBBB	ICD	CRT-D	CRT-P or CRT-D	CRT-P
≥150 milliseconds with or without LBBB	CRT-D	CRT-D 1 Guidance	CRT-P or CRT-D	CRT-P
LBBB, left bundle branch block; NYHA, New York Heart Association				

Figure 7- Treatment options with ICD or CRT for people with Heart Failure who have left ventricular dysfunction with an LVEF of 35% or less (according to NYHA class, QRS duration and presence of LBBB [103]

1.7 Predictive and Prognostic Modelling in Heart Failure

Outcomes in Heart Failure remain poor and highly variable. [126]As a result, risks amongst different subgroups of patients vary and change over time. It is important for patients and their families to understand these risks as well as disease trajectory over time. [127] [128] Knowledge of these risks can also result in better informed decisions about the initiation and intensity of treatment, device therapy and end of life care according to the individual patient need and potential for benefit. [129] [130] Patients' and clinicians' judgement on risk can be inaccurate and highly variable [131] and for complex conditions such as Heart Failure, single predictors of risk are not sufficient as accurate estimators [133] Therefore multivariable statistical models are a possible solution as they estimate risk from a combination of several predictors. [132] [133]

According to the European Society of Cardiology, there are four prognostic risk scores which estimate all-cause mortality with fully published information on estimators and missing data. There were the Seattle Heart Failure Model (SHFM), The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure (GISSI-HF), Meta-analysis Global Group in Chronic

Heart Failure (MAGGIC) and the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM). [134]

1.7.1 Seattle Heart Failure Model

The Seattle Heart Failure Model is a prognostic model derived from The Prospective Randomized Amlodipine Survival Evaluation cohort (PRAISE1) which is a cohort of 1125 Heart Failure Patients. PRAISE1 was a randomized controlled trial of amlodipine versus placebo among 1153 patients in the United States and Canada with ejection fraction (EF) <30% and New York Heart Association (NYHA) functional class IIIB to IV. 32 patients were excluded due to incomplete baseline data. [135] In this model, clinical variables associated with mortality were evaluated with a cox proportional hazards model. For medications and devices not available in the derivation database, hazard ratios were estimated from published literature.

The SHFM has been prospectively validated in 5 additional cohorts of 9942 participants in total.[136]The first was ELITE2 (Evaluation of Losartan in the Elderly), a randomized trial of captopril versus losartan among 3152 patients in 46 countries with EF ≤40%, age ≥60 years, and NYHA class II to IV Heart Failure. They excluded 165 patients from ELITE2 due to incomplete baseline data.[137] The second validation cohort was the Valsartan Heart Failure Trial (Val-HeFT), a randomized trial of valsartan versus placebo in 5010 patients in 16 countries with EF ≤40 and NYHA class II to IV Heart Failure. One patient was excluded in this cohort due to probable data entry error. [138]The third validation cohort was from the University of Washington (UW), a prospective cohort of 148 consecutive outpatients at a tertiary US outpatient clinic. The fourth validation cohort was the Randomized Enbrel North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) was a randomized trial of etanercept in 925 patients with NYHA class II to IV Heart Failure and EF ≤30 in the United States and Canada. [139] The fifth validation cohort was the Italian Heart Failure Registry (IN-CHF) which was composed of 2411 patients without any exclusion criteria.

In total, they evaluated 22 predictors excluding 9 medications and devices for which hazard ratios were collected from previous randomised trials. The final model predicted a 1-year and 2-year survival rate of 73.4% and 56.7% in the PRAISE1 cohort which was comparable to the actual survival rates which were 74.3% and 56.0%. The correlation between predicted and actual survival by deciles was 0.97. [136]In the ELITE2 cohort, the final model predicted 1- and 2-year survivals for the entire cohort which were 90.5% and 82.4% versus actual survival of 88.5% and 80.0%. The correlation between predicted and actual survival by deciles was 0.97. In the Val-HeFT cohort, the predicted 1-, 2-, and 3-year survivals for the entire cohort were 90.9%, 83.3%, and 76.8% versus actual survival of 91.0%, 81.6%, and 71.7%. The correlation between predicted and actual survival by deciles was 0.98. In the UW cohort, the predicted 1-, 2-, and 3-year survivals for the entire cohort were 86.5%, 76.5%, and 68.6% versus actual survival of 86.5%, 79.7%, and 71.8%. The correlation between predicted and actual survival by quintiles was 0.99. In RENAISSANCE, the predicted 1- and 2-year survivals for the entire cohort were 83.8% and 72.3% versus actual survival of 83.3% and 65.4%. The correlation between predicted and actual survival by quintiles was 0.97. In IN-CHF, the predicted versus actual 1-year survivals for the entire cohort was 89.6% versus 86.7%. The correlation between predicted and actual survival by quintiles was 0.99. The 6 datasets were then combined and compared for survival. The SHFM predicted 1-, 2-, and 3-year survivals were 88.2%, 79.2%, and 71.8% versus actual survival of 87.8%, 77.6%, and 68.0%. The correlation between predicted and actual survival by quintiles was 0.98. [136]

When regards to 1-year ROC, PRAISE1 had a value of 0.725(95%CI, 0.69 to 0.76), ELITE2 had a value of 0.682(95%CI, 0.65 to 0.73), UW had a value of 0.810(95%CI 0.72 to 0.90), RENAISSANCE had a value 0.682(95%CI, 0.63 to 0.73) Val He-FT had a value 0.694(95%CI 0.682 to 0.72) and IN-CHF which had a value of 0.749(95%CI, 0.70 to 0.80). All data sets were also combined which then provided a ROC of 0.729(95%CI, 0.714 to 0.744). [136]

The SHFM predicts survival well and is validated against a range of countries, ages, and Heart Failure stages. The score also indicated that NYHA class, ischemic aetiology, diuretic dose, EF, SBP, sodium, haemoglobin, percent lymphocytes, uric acid, and cholesterol each had independent predictive power. The Seattle Heart Failure Model also had a higher ROC than the previously developed ADHERE or Toronto models of Heart Failure when applied to the same data sets. The model incorporates the use of medications and devices and predicts the associated change in survival. Whilst this was a useful feature of this model, the fact that they used hazard ratios from other clinical trials is problematic. This is because results from prior clinical trials may not be generalizable to a wider population of Heart Failure patients and their hazard ratios would not have been adjusted for all other predictors. [136]

The Seattle Heart Failure Model was developed and validated among outpatients participating in clinical trials, observational studies, or clinical registries, and the model may not be generalizable to hospitalized patients or those with major life-altering comorbidities such as cirrhosis, renal failure, dementia, or cancer.[140]

1.7.2 Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure

The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico - Heart Failure (GISSI-HF) score is a prognostic model derived from the GISSI-HF study which was composed of 6975 patients with chronic Heart Failure followed up for a period of four years with information collected on pharmacological treatment, medical history, and biochemical measurements. This cohort of patients were recruited from a national network involving 326 cardiology and 31 internal medicine departments across Italy. In this model, clinical variables associated with mortality were evaluated with a cox proportional hazards model. [141]

The model was internally validated and evaluated through CPE index and C-statistics, with the original model attaining a CPE index for predicting mortality of 0.70 and a C-statistic of 0.76. Results of internal validation revealed no

overoptimism in the predictive discrimination of the final reduced model (Dxy index, –0.4645), with this index remaining unchanged at –0.4566 (optimism, –0.0079) with bootstrap techniques. When compared to the SHFM on the GISSI-HF database, the performance of the GISSI-HF model was similar with a C-statistic of 0.737 compared to 0.73, respectively. Furthermore, the prognostic contribution of the additional variables in the GISSI-HF model on top of the Seattle model, evaluated either in terms of difference in C statistics (P<0.001) or by NRI, was statistically significant (P<0.001), suggesting that the GISSI-HF model has the advantage compared with the Seattle model in terms of discrimination. [141]

The study itself identified 25 independent predictors of mortality, with the most important being NYHA class, eGFR, LVEF, COPD, sex, SBP, diabetes mellitus, haemoglobin level, uricemia, aortic stenosis, and body mass index. At the time of publication, the study was the largest cohort of patients receiving contemporary pharmacological treatment, followed for a long period (median, ≈4 years) and collecting enough fatal events to allow reliable subgroup analyses. The study was also the second (after the CORONA study) to look at routine biochemical measurements as well as the only study in it's time to include HF patients regardless of age (>18 years), aetiology, and LVEF. [141]

The study established age, NYHA class, eGFR and reduced ejection fraction as the strongest predictors, in line with previous studies. COPD, Aortic Stenosis, and low body mass were also found to be important risk factors with prognostic roles also evidenced with decreasing levels of haemoglobin and increasing uricemia (above a threshold of 6.9 mg/dL) for mortality. [141]

The GISSI-HF model was built on a large database of patients from a multi-centre clinical trial and therefore provides a realistic picture of clinical practice. However, all participating hospitals were based in Italy and as such the model may only be representative of the Italian population. The lack of validation of the model in an external population can only lend to support this conclusion. This brings into question the generalizability of the model in different parts of

the world, particularly because of the different approaches to HF care across the globe. [141]

1.7.3 Meta-analysis Global Group in Chronic Heart Failure

The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) model is a prognostic model developed from individual patient data from 31 cohort studies. Six of these were randomized controlled trials (24 041 patients) and 24 were registries (15 331 patients). 39,372 patients were included in total, with 31 baseline predictors of mortality considered. Unlike the previous models which used Cox regression, the MAGGIC model is built on Poisson regression with patient survival as an outcome. They adjusted for study (random effect) and follow-up time (due to higher mortality rate in early follow-up) and identified 13 independent predictor variables. These were age, gender, BMI, smoker status, systolic blood pressure, diabetes, New York Heart Association (NYHA) Classification, COPD, ejection fraction, Heart Failure duration, creatinine, beta-blocker, and ACE inhibitor. The model also accounted for interaction between ejection fraction and age as well as ejection fraction and SBP. [142]

The model was not formally validated or evaluated against an external cohort in the original study however, given the wide variety of different studies included, with a global representation, its findings could be considered to be generalizable to a broad spectrum of current and future patients. A limitation to this methodology however is the fact that many cohorts were missing variables which were then imputed. BMI and HF duration, for example, had 17 and 20 studies respectively with missing data which is a substantial number of studies out of the total of 31 to have imputed. [142]

1.7.4 Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) prognostic model is a cox-regression model built on data from the CHARM programme. This programme included 7601 patients (7599 with data) with a clinical diagnosis of CHF, irrespective of left ventricular

ejection fraction (EF). The programme itself had stringent conditions with patients aged 18 or older who had symptomatic CHF of at least 4 weeks duration being eligible and those with serum creatinine ≥265 µmol/L, serum potassium ≥5.5 mmol/L, myocardial infarction or stroke in the prior 4 weeks, or non-cardiac disease judged to limit 2-year survival ineligible. The programme consisted of three component trials that shared these inclusion and exclusion criteria, endpoint definitions, and follow-up methods. Patients were enrolled with (i) left ventricular EF>40% (CHARM-Preserved) (ii) ACE-inhibitor intolerance (CHARM-Alternative) and left ventricular EF≤40%, and (iii) ACE-inhibitor (CHARM-Added) and left ventricular EF≤40%. The primary combined endpoint of each constituent trial was time to cardiovascular (CV) death or hospitalization for the management of worsening HF and the primary endpoint of the overall programme was all-cause mortality. [143]

For all-cause mortality, the study identified 21 independent predictors which included age, diabetes, ejection fraction and NYHA class amongst others. This was the first prognostic model to stratify by BMI groupings and found that patients whose BMI is below the median of 27.5 kg/m2 have a 9.3% increase in mortality hazard for each 1 kg/m2 reduction from a BMI of 20 kg/m2, P<0.000000001. Those with BMI of ≥27.5 kg/m2 when compared carry a 67% increased risk. This supports the U-shaped association regularly referenced in studies when looking at the relationship between BMI and mortality in Heart Failure patients. [144]

The model was internally validated and evaluated through C-indices (areas under the receiver operating characteristics curve) for predicting the 2-year incidence of death and attained a value of 0.75. Results of internal validation revealed no 'over-optimism' in the predictive discrimination with C-indices of 0.74 using the re-fitted model. [143]

At the time of publication, this model was the first to be developed in a single cohort spanning the full range of left ventricular systolic function, including a substantial proportion of patients with preserved left ventricular EF. The model performed equally well in patients with low and preserved EFs. The study also

noted there to be a non-linear relationship between age and mortality, where age had relatively little impact on outcome until after age 60, and then the risk of death increases nearly two-fold every 10 years. [143]

In total the CHARM model was based on many patients and events across a broad spectrum of HF, thus allowing a more detailed, precise, and generalizable evaluation of predictors and their independent contributions. However, like most clinical trial databases, it was highly selective with patients at high risk and one in four patient's dead with a median follow-up of 38 months. In addition to this, the model did not use measurements of blood laboratory tests which are known to be important predictors of outcome nor was the model validated on an external dataset – all of which would have increased its generalisability to a clinical context. [143]

1.8 Rationale of Thesis

Heart Failure constitutes a major public health problem which remains highly prevalent in the UK and globally [145]. It is associated with substantial health, social and economic/financial burden, and is associated with an increased risk of mortality.

Many risk factors for Heart Failure are known, such as ischemic heart disease, hypertension, diabetes, dyslipidaemia, and smoking. These risk factors are also known to increase morbidity and mortality. Additional predictors of mortality include age, NYHA class, ejection fraction, systolic blood pressure, routine biochemical measurements, use of certain medications, presence of comorbidities and BMI.

The effect of BMI on Heart Failure prognosis is unclear with some studies suggesting that a BMI greater than 30 can double the risk of Heart Failure [146] and other studies showing that obese patients have a lower risk of death than individuals of normal weight. This is known as the obesity paradox and is a key issue within the management of heart failure today.

Guidelines exist for HF management but no clinical guidelines in use to guide health care professionals in determining those at increased risk of mortality. Several predictive models exist but due to several limitations, clinical utility of these in the UK are limited. This is mainly due to their lack of external validation. In addition to this, many were based on clinical trial participants with a limited range of predictors and/or specific inclusion criteria that made their results non-generalisable.

This thesis therefore aims to build on previous prognostic models on Heart Failure mortality, by developing and validating developing an appropriate tool for clinical use in the United Kingdom (UK) in addition to determining the effect of obesity on Heart Failure prognosis.

2 Objectives

The main objective of this study is to develop and validate a prognostic model to predict the risk of mortality in patients with Heart Failure and to determine the relationship between BMI and mortality in adults who are diagnosed with Heart Failure.

Objectives relating to the aim are:

1. Determine predictors of mortality in 1-year in individuals with HF, and then develop a predictive algorithm for HF using multivariable Cox-Regression modelling.

2. Investigate the validity of the HF predictive algorithm through bootstrapping 200 samples of the derivation data and estimating optimism across both models.

3. Determine the effect of obesity on Heart Failure prognosis by stratifying the model by BMI groupings. This sheds light on the 'obesity paradox' that is an ongoing issue in heart failure research and management.

3 Methods

3.1 Design

The study is a retrospective cohort study.

3.2 Data Source

The setting of the study is primary care practices that are providing data to the CRPD database (CPRD Aurum). The CPRD database is an ongoing primary care database of anonymised medical records that covers over 19.3 million patients from 738 practices in the UK.

3.2.1 Structure of the CPRD database

The CPRD database (CPRD Aurum) captures symptoms, prescriptions, diagnoses, tests, immunizations, lifestyle factors and referrals recorded by the GP or other practice staff daily and is processed to create monthly snapshots for observational research. The database structure is based on eight files (Figure 1). The patient file records patient demographics, details on when the patient registered/deregistered from the practise and date of death if applicable. The practice file contains the practice region and the most recent date of data collection for the practice. The staff file contains the job category for each staff member in CRPD Aurum. The consultation file holds information relating to the type of consultation i.e., telephone or home visit. The observation file contains medical-history data entered on the GP system including symptoms, clinical measurements, laboratory test results, diagnoses, and demographic information. Observations that occur during a consultation are linked via the consultation identifier. The data is structured in long format and observations are linked via a parent observation. The referral and problem files are linked to the observation file and contain extra data for referral and problem type observations. The problem file contains the details of the patient's medical history that have been defined as a problem and the referral contains information involving referrals. GP's use 'problems' to manage chronic conditions, which enables them to group clinical events by problem as opposed to consultation date. The drug issue file contains data relating to all prescriptions issued by the GP and are linked back to problems.[147]

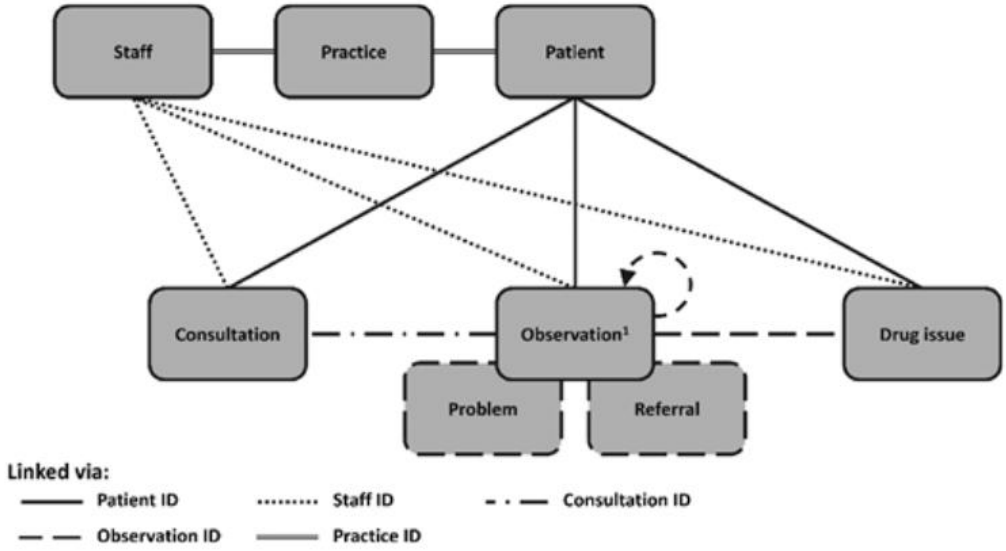


Figure 8-CRPD Aurum dataset structure [147]

3.2.2 Quality of data in the CPRD database

There are over 900 checks that cover the integrity, structure and format of the data collected into CPRD Aurum. Issues highlighted by this quality assurance process are reviewed before the data is incorporated into CPRD Aurum. [147]

There are three types of validation that takes place with CPRD Aurum data. Collection-level validation ensures integrity by checking that data received from EMIS Web® practices contain only expected data files and ensures that all data elements are of the correct type, length, and format. Transformation-level validation checks for referential integrity between records to ensure that there are no orphan records included in CPRD Aurum (e.g., that all event records link to a patient). Research-quality-level validation is the last level and covers the actual content of the data. CPRD provides a patient-level data quality metric in the form of a binary 'acceptability' flag. This is based on recording and internal consistency of key variables including date of birth, practice registration date and transfer out date. Duplicate records are also identified and removed. [147]

Research using CPRD data has informed drug safety guidance and clinical practice and resulted in over 2,500 peer-reviewed publications. [148]

3.2.3 Strengths and weaknesses of the CPRD Database

3.2.3.1 Strengths

CPRD Aurum covers 13% of the population of England and is representative of the population in terms of geographical spread, deprivation, age, and gender. Patient level data from the database has been linked to secondary care and other datasets, providing a fuller picture of the patient care pathway and outcomes. All CPRD Aurum practices have consented to participating in the linkage scheme, which includes data from national secondary care databases (hospitals and mental health service providers), the national cancer registry, death registrations and deprivation measures. [147]

3.2.3.2 Weaknesses

Primary care records are well known to have incomplete data and techniques such as imputation may be necessary to deal with missingness and to resolve discrepancies in measures between consultations. In addition to this, these records and their subsequent analysis interpret the absence of a read code for a given disease to correspond to the absence of disease itself. [149]

Read code lists and algorithms need to be developed for each study to identify exposures and outcomes of interest and this can lead to inconsistent definitions (and therefore results) between studies using the same data. [149]

General practices receive information about patient contacts with secondary care regularly, however, must be manually entered into the patient record. Therefore, details about hospital admissions (dates, diagnoses, tests performed, length of stay) may be incomplete. [149]

Many patient groups are also missing from public primary care records. This includes patients who use private health care, prisoners, the homeless and some patients in care homes. Many prescriptions of drugs may take place outside of primary care. [149]

3.3 Participants

The study population comprises of all patients who meet the following inclusion criteria:

- 18 years and over at study start date
- Have been diagnosed with Heart Failure.
- Registered for at least a year after the earliest date which the CPRD practice started contributing up-to-standard data (baseline data for study entry) to the most recent data available in CPRD (2018).

Patients enter the cohort at the time of first ever record of Heart Failure on or after 1st Jan 2005, and the follow-up ends at the earliest of any of the following dates: the study end on 31st December 2018; patient transferred out of the practice (any cause); last collection date for the practice; or death.

Read codes for heart failure are detailed in Appendix 2.

3.3.1 Eligibility criteria for Heart Failure patients in this study

Adults (over 18 years of age) with new diagnosis of Heart Failure identified from general practices with linked secondary care records from Hospital Episode Statistics (HES). Individuals had to be actively registered for at least one year before the study start date (before the date of HF diagnosis).

3.4 Exclusion criteria

The following patients were excluded from the study population:

- Patients diagnosed with Heart Failure after death
- Patients with less than one year of active records before HF diagnosis
- Patients who had transferred practice before heart failure diagnosis

3.5 Outcome

The main outcome for this study is all-cause mortality at 1 year defined as death within 12 months after diagnosis with heart failure.

3.6 Predictors

Predictors such as age and gender were explored. Other predictors include BMI, NYHA class, systolic blood pressure, left ventricular hypertrophy, history of hypertension, history of myocardial infarction, history of cerebrovascular disease, history of chronic obstructive pulmonary disease, diabetes, use of diuretics, use of digoxin, use of a calcium-channel blocker, use of lipid-lowering

agents, use of an angiotensin-converting enzyme (ACE) inhibitor, use of a β-blocker, creatinine, bilirubin, CRP , presence of anaemia, , cardiomyopathy, dyspnoea at rest, type-2 diabetes mellitus, albumin, race, coronary heart disease, , cancer history, alcohol use, smoking status, SBP, eGFR, , serum albumin, , total cholesterol levels, HDL, LDL, VLDL , jugular venous pressure, pulmonary congestion, atrial fibrillation, chronic kidney disease.

These predictors were measured and recorded before diagnosis with heart failure in GP databases or linked datasets.

3.7 Sample size

The study analysed information on 109,577 patients diagnosed with Heart Failure over a 12-month follow up failure from 1 January 2000 to 31 December 2017 from the Clinical Practice Research Datalink. This sample size was arrived at through adherence to the inclusion and exclusion criteria.

3.8 Missing Data

For categorical clinical variables (such as diabetes and chronic kidney disease) which are missing or not recorded, common assumption was made to give these individuals the null values – for instance, 'no diabetes' or 'no chronic kidney disease'.

Multiple imputation with chained equations were used to estimate missing values. Variables included in the imputation model were age, gender, NYHA class, systolic blood pressure, left ventricular hypertrophy, history of hypertension, history of myocardial infarction, history of cerebrovascular disease, history of chronic obstructive pulmonary disease, diabetes, use of diuretics, use of digoxin, use of a calcium-channel blocker, use of lipid-lowering agents, use of an angiotensin-converting enzyme (ACE) inhibitor, use of a β-blocker, presence of anaemia, , cardiomyopathy, dyspnoea at rest, type-2 diabetes mellitus, albumin, race, coronary heart disease, , cancer history, alcohol use, smoking status, pulmonary congestion, atrial fibrillation, chronic kidney disease. Variables imputed were BMI, creatinine, bilirubin, CRP, SBP,

eGFR, serum albumin, total cholesterol levels, HDL, LDL, VLDL and jugular venous pressure.

If the models failed to converge, an alternative technique such as predictive mean matching was used. All other patient variables with no missing records/values were included as auxiliary variables in the imputation models to improve prediction. Ten imputed datasets were created.

To assess the robustness of the missing-completely-at-random (MCAR) assumption, little's test for MCAR was used. [150]

3.9 Statistical Analysis and Methods

3.9.1 Assessing Baseline Characteristics

Baseline characteristics were obtained through a process of variable extraction from the CPRD database and then completion of univariable analysis in both groups of patients (died during the follow up period of 12 months or did not die during the follow up period). Univariable analysis included observing summary statistics for each variable and testing for significant differences between both exposure groups. For significance testing, the chi-squared test was used for categorical variables, the Chi-Squared Test for trend for ordered categorical variables, the T-Test for normally distributed continuous variables and the Wilcoxon Rank Sum test for non-normally distributed continuous variables.

Continuous predictors were modelled as linear. The cut-off point for categorical predictors was at the point of heart failure diagnosis.

3.9.2 Assessing Mortality Rate

Mortality rates were assessed per 1000 person months for the categorical variables of gender, age, BMI, region, race, New York Heart Association Classification (NYHA) and prior history of atrial fibrillation, anaemia, cardiomyopathy, cerebrovascular disease, coronary heart disease, chronic kidney disease, chronic obstructive pulmonary disease, cancer, dyspnoea, hypercholesterolaemia, hypertension, left ventricular hypertrophy, pulmonary congestion, smoking, and type-2 diabetes.

3.9.3 Kaplan-Meier Graphs

Kaplan Meier graphs were developed for the same variables assessed for mortality rate, with significance testing for equality of survival distributions (the Log-Rank test).

3.9.4 Cox-regression modelling

3.9.4.1 Determination of predictors of HF Mortality

The full list of potential predictors was derived based on a literature review and discussions with clinical experts. Predictors which were poorly reported on CRPD were not included. We classified patients as having a particular predictor if there was a record of the relevant clinical code (s) in their general practice record.

3.9.4.2 Derivation of risk prediction model

For the derivation of the risk prediction model, all candidate predictor variables at a less than 0.02 significance level were used in a multivariable Cox regression model. Unadjusted association between each predictor and outcome were reported. Through backwards elimination, candidate predictor variables from the multivariable model were determined after assessment of model fit using the BIC/AIC. Retention of variable in the model occurred if the AIC or BIC does not result in a significant difference in model fit. Risk equations for predicting the all-cause mortality were formed using the estimated β multiplied by the corresponding predictors included in the model together with the average intercept across patients. This process led to an equation for the predicted 1-year absolute risk of all-cause mortality. Hazard ratios for each significant predictor of mortality were reported. Interaction terms were not assessed in the model. Proportionality of hazards for categorical variables were tested through Kaplan-Meier curves.

3.9.4.3 Validation

The performance of the model was assessed through the C-statistic and calibration slope (where 1.00 is the ideal). The C-statistic represents the probability that for any randomly selected pair of patients, one with all-cause mortality and another without all-cause mortality, the proportion of such pairs in which the individual who experienced a positive outcome had a higher

predicted probability of experiencing the outcome than the individual who did not experience the positive outcome. After this, an internal validation was completed to correct measures of predictive performance for optimism (overfitting) by bootstrapping 200 samples of the derivation data. The model derivation process was repeated in each bootstrap sample (as previously outlined, including variable selection) to produce a model, apply the same bootstrap sample to quantify apparent performance, and apply the model to the original dataset to set model performance (calibration slope and C statistic) and optimism (difference in test performance and apparent performance). The overall optimism across all models was then estimated (for example, derive shrinkage coefficient= average calibration slope from each of the bootstrap samples). To account for overfitting during the development process, the original β coefficients were multiplied by the uniform shrinkage factor in the final model. At this point, the intercept was re-estimated based on the shrunken β coefficients to ensure that the overall calibration is maintained and produce a final model. There were no differences in setting, eligibility, criteria, predictors and outcomes between the development and validation datasets.

3.10 Risk Groups

The cohort was then split into even quartiles based on predicted risk scores. These risk groups ranged from one to four with one indicating the quartile of scores with the lowest risk. Kaplan Meier curves were then produced for each group. The Royston D-statistic was then be used to assess the discrimination of these quartiles by quantifying the observed separation between these groups. [151]

The study adhered to the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) statement for reporting. [152]

3.11 Use of linked data

The study population from CRPD GOLD was linked to Hospital Episode Statistics (HES) Admitted Patient Care, Office of National Statistics (ONS) Death Registration Data and Patient Level Index of Multiple Deprivation (IMD).

Linkages to Hospital Episode Statistics was used for case ascertainment of Heart Failure and comorbid conditions such as myocardial infarction, stable and unstable angina, stroke, transient ischaemic attack (TIA), peripheral vascular disease (PVD) or T2DM.

Linkage to ONS death registration was used to determine mortality and cause of mortality. Patient date of death was confirmed using the ONS death date and where there is a discrepancy between both dates, the ONS date was applied in the dataset.

Patient level IMD-linkage was used as covariate in the prediction models.

3.12 Preparation of datasets

For this thesis, data management and cleaning of the CPRD AURUM database was performed by Habibullah Muhammad-Kamal under the supervision of Dr Stephen Weng and Dr Barbara Iyen. Read code lists were compiled by Habibullah Muhammad-Kamal for Heart Failure and all apriori predictors for mortality found within the literature.

3.13 Feasibility

In a previous study [153] using the Clinical Practice Research Datalink (CPRD), there were 55,959 patients aged 45 and over with a new diagnosis of Heart Failure from 1 January 2000 to 31 December 2017 and linked to inpatient Hospital Episode Statistics and Office for National Statistics mortality data. There were 30 906 deaths in the Heart Failure group over the study period of up to 10 years.

3.14 Sample size considerations

Simulations on binary outcomes time-to-event sample size calculations showed that events per predictors can range from 4.8 to 23 cases in certain conditions. Using a top-end conservative estimate of 23 cases per predictor, a maximum 50 predictors explored, the number of events needed could be as high as 1,150. Given that the outcome of all-cause mortality is common in HF patients with approximately 50% mortality rate over 10 years from previous studies, this analysis was sufficiently powered.[154]

3.15 Software

All analysis was completed on STATA SE 16 (StataCorp LP, Texas, USA).

3.16 Study Ethics

Ethical approval for this study was granted by the CPRD Independent Scientific Advisory Committee (ISAC) (protocol number 19 274R). All records of patients in CPRD are anonymised and do not contain any identifying information such as name, address, exact date of birth and NHS number.

3.17 Funding

This research was funded generously by the Aziz Foundation master's scholarship grant.

3.18 Outcomes to be measured

As this study main purpose is to derive and validate a multivariable prediction model. Covariate selection and model adjustments were made during the model building phase and the model was evaluated by the Area Under the Receiver Operating Curve (AUROC) which is the main outcome measured.

4 Results

The study analysed information on 109,577 patients diagnosed with Heart Failure over a 12-month follow up failure from 1 January 2000 to 31 December 2017 from the Clinical Practice Research Datalink (CPRD). Table 1 summarises the basic characteristics of the study population.

4.1 Participants

4.1.1 Mortality rate by patient characteristics

Mortality rates were stratified by different exposure groups in the cohort, this is summarised in Table 1.

Exposure	Deaths	Person-Months	Mortality rate per 1000 person-months (95%CI)	Total
n	16,437	$1.2e^3$	13.87(13.66 to 14.08)	109,577
Gender				
Male	8058	651.65	12.37 (12.10 to 12.64)	59,476
Female	8379	533.50	15.71 (15.37 to 16.05)	50,101
Age category				
Under 40	33	15.56	2.12 (1.51 to 2.98)	1,376
40-49	105	32.53	3.23 (2.67 to 3.91)	2,809
50-59	340	91.66	3.71 (3.34 to 4.13)	7,907
60-69	1139	196.64	5.79 (5.47 to 6.14)	17,144

70-80	3465	342.27	10.12 (9.79 to 10.47)	30,564
Over 80	11355	506.49	22.42 (22.01 to 22.84)	49,777
BMI category				
Underweight (<18)	230	7.10	32.40 (28.47 to 36.87)	750
Normal weight (18-24.9)	6226	233.51	26.66 (26.01 to 27.33)	23,462
Pre-obesity (25-29.9)	7730	591.51	13.07 (12.78 to 13.36)	54,343
Obesity Class I (30-34.9)	1914	294.88	6.49(6.21 to 6.79)	25,924
Obesity Class II (35-39.9)	250	58.15	5.80 (5.21 to 6.45)	5,098
Obesity Class III (>40)	87	13.05	6.66(5.40 to 8.22)	1,150
Region				
North East	212	14.50	14.62 (12.78 to 16.73)	1351
North West	1649	123.79	13.32 (12.69 to 13.98)	11,426
Yorkshire and Humber	615	39.036	15.76 (14.56 to 17.05)	3,681
East Midlands	412	34.83	11.83 (10.74 to 13.03)	3,173
West Midlands	1379	97.48	14.15 (13.42 to 14.91)	9,028
East of England	1027	70.29	14.61 (13.75 to 15.53)	6,567

South West	1300	88.43	14.70 (13.92 to 15.52)	8,254
South Central	1366	92.66	14.74 (13.98 to 15.55)	6,567
London	2012	142.55	14.12 (13.51 to 14.75)	8,254
South East Coast	1239	93.06	13.32 (12.59 to 14.08)	8,596
Northern Ireland	530	39.33	13.48 (12.38 to 14.68)	13,225
Scotland	2589	193.00	13.41 (12.91 to 13.94)	17,704
Wales	2030	150.50	13.49 (12.91 to 14.09)	13,882
Unknown	77	5.71	13.48 (10.78 to 16.86)	517
Racial category				
White racial category	21	1.81	11.57 (7.55 to 17.75)	166
Bangladeshi racial category	0	0.02		
Mixed racial category	0	0.01		
Chinese racial category	0	0.05		
Afro-Caucasian racial category	0	0.01		
Afro-Caribbean racial category	3	0.21	14.07 (4.54 to 43.63)	19
Arab racial category	0	0.01		
Pakistani racial category	0	0.01		
Unknown racial category	16413	$1.2e^{3}$	13.87 (13.66 to 14.08)	109,381

New York Heart Association (NYHA) functional classification				
NYHA Class 1	19	8.14	2.34 (1.49 to 3.66)	687
NYHA Class 2	82	15.52	5.28 (4.25 to 6.56)	1339
NYHA Class 3	86	7.98	10.77 (8.72 to 13.31)	715
NYHA Class 4	15	0.55	27.30 (16.46 to 45.28)	61
Unclassified	16235	1.2 e^3	0.0140811 (0.0138662 to 0.0142994)	106,775
Prior history of atrial fibrillation				
No	10245	775.74	13.21 (12.95 to 13.47)	71,453
Yes	6192	409.41	15.12 (14.75 to 15.51)	38,124
Prior history of anaemia				
No	12590	987.60	12.75 (12.53 to 12.97)	90,633
Yes	3847	197.55	19.47 (18.87 to 20.10)	18,944
Prior history of cardiomyopathy				
No	16150	1100	14.22 (14.00 to 14.44)	105,275
Yes	287	49.13	5.84 (5.20 to 6.56)	4,305

Prior history of cerebrovascular disease				
No	14566	1100	13.40 (13.18 to 13.62)	100,166
Yes	1871	97.91	19.11 (18.26 to 20.00)	9,411
Prior history of coronary heart disease				
No	13467	915.33	14.71 (14.47 to 14.96)	85,339
Yes	2970	269.83	11.01 (10.62 to 11.41)	24,238
Prior history of chronic kidney disease				
No	10932	893.85	12.23 (12.00 to 12.46)	81,812
Yes	5505	291.31	18.90 (18.41 to 19.40)	27,765
Prior history of chronic obstructive pulmonary disease				
No	15506	1100	13.79 (13.58 to 14.01)	103,934
Yes	931	60.95	15.28 (14.33 to 16.29)	5,643
Prior history of cancer				
No	374	17.93	20.86 (18.85 to 23.09)	1,838
Yes	16063	1200	13.76 (13.55 to 13.98)	107,739
Prior history of dyspnoea				

No	15092	1100	13.73 (13.51 to 13.95)	101,606
Yes	1345	85.90	15.66 (14.84 to 16.52)	7,971
Prior history of hypercholesterolaemia				
No	14939	1100	14.07 (13.85 to 14.30)	98,331
Yes	1498	123.34	12.15 (11.55 to 12.78)	11,246
Prior history of hypertension				
No	8816	658.25	13.39 (13.12 to 13.68)	60,772
Yes	7621	526.90	14.46 (14.14 to 14.79)	48,855
Prior history of left ventricular hypertrophy				
No	16130	1200	13.92 (13.71 to 14.14)	107,168
Yes	307	26.60	11.54 (10.32 to 12.91)	2,409
Prior history of pulmonary congestion				
No	16401	1200	13.86 (13.65 to 14.07)	109,403
Yes	36	1.78	20.28 (14.63 to 28.11)	174
Prior history of smoking				
No	5672	327.79	17.30 (16.86 to 17.76)	31,375

Yes	10765	857.36	12.56 (12.32 to 12.80)	78,802
Prior history of type-2 diabetes mellitus				
No	12834	933.69	13.75 (13.51 to 13.99)	86,314
Yes	3603	251.46	14.33 (13.87 to 14.80)	23,263

Table 1- Mortality rates by patient characteristics

For imputed variables; BMI had 15.7% of records missing, GFR had 39.7% of records missing, JVP had 99.5% of records missing, CRP had 63.0% of records missing, creatinine concentration had 15.2% of records missing, VLDL had 99.4% of records missing, LDL had 38.8% of records missing, HDL had 30.5% of records missing, total cholesterol had 22.4% of records missing, systolic blood pressure had 5.6% of records missing, bilirubin concentration had 11.2% of records missing and albumin concentration had 22.0% of records missing. All other missing records are detailed in Table 1. The outcome (mortality) did not have any missing records.

When stratified by gender, females have a rate of mortality of 12.37 per 1000 person-months (95%CI 12.10 to 12.64) which is higher than the mortality of males which is 15.71 per 1000 person-months. As shown in Table 2, mortality rates increased with increasing age such that the rate in patients with Heart Failure under the age of 40 was 2.12 per 1000 person-months (95% CI 1.51 to 2.98), and the rate in this above 80 years of age was 22.42 per 1000 person-months (95%CI 22.01 to 22.84).

When stratified by BMI, individuals with obesity classes I, II and III had the lowest mortality rates, with individuals with an obesity class of III having the highest of the group with a mortality rate of 6.66 per 1000 person-months (95%CI 5.40 to 8.22). In contrast, patients who were underweight had the highest mortality rate which was 32.40 per 1000 person-months (95%CI 28.47

to 36.87). This was followed by patients with a normal BMI, who had a mortality rate of 26.66 per 1000 person-months (95%CI 26.01 to 27.33). Patients classed as pre-obesity had the third highest mortality rate with 13.07 per 1000 person-months (95%CI 12.78 to 13.36). Patients who were classed as obesity class I had a mortality rate of 6.49 per 1000 person-months (95% CI 2.67 to 3.91) whilst patients classed as obesity class II had a mortality rate of 5.80 per 1000 person-months (5.21 to 6.45).

When stratified by Region, there was no observable pattern to mortality rates and many confidence intervals overlapped. Patients who lived in Yorkshire and Humber had the highest mortality rate which was 15.76 per 1000 person-months (95%CI 14.56 to 17.05). This was followed by patients in South Central, who had a mortality rate of 14.74 per 1000 person-months (95%CI 13.98 to 15.55). Patients in South West had the third highest mortality rate with 14.70 per 1000 person-months (95%CI 13.92 to 15.52). This was followed by patients in the North East, who had a mortality rate of 14.62 per 1000 person-months (95%CI 12.78 to 16.73). Patients in the East of England had the fifth highest mortality rate of 14.61 per 1000 person-months (95% CI 2.67 to 3.91) whilst patients in West Midlands followed with a mortality rate of 14.15 per 1000 person-months (13.42 to 14.91). Patients in the London had the seventh highest mortality rate of 14.12 per 1000 person-months (95% CI 13.51 to 14.75) whilst patients in Wales followed with a mortality rate of 13.49 per 1000 person-months (12.91 to 14.09). Patients in the Northern Ireland had the ninth highest mortality rate of 13.48 per 1000 person-months (95% CI 12.38 to 14.68) whilst patients in Scotland followed with a mortality rate of 13.41 per 1000 person-months (12.91 to 13.94). Patients in the North West and the South East Coast had the joint 11th highest mortality with 13.32 however the North West having a 95% CI between 12.69 and 13.98 whilst the South East Coast had a 95%CI between 12.59 to 14.08. The East Midlands had the lowest mortality rate with 11.83(95%CI 10.74 to 13.03).

When stratified by Racial Category, only patients classed as White, and Afro-Caribbean had mortality rates recorded. patients who were classed as Afro-

Caribbean had the highest mortality rate which was 14.07 per 1000 person-months (95%CI 4.54 to 43.63). This was followed by patients who were classed as White, who had a mortality rate of 11.57 per 1000 person-months (95%CI 7.55 to 17.75).

When stratified by NYHA class, mortality rate increased with classification. Patients with a NYHA class of 4 had the highest mortality rate which was 27.30 per 1000 person-months (95%CI 16.46 to 45.28) whilst patients with an NYHA class of 1 had a mortality rate of 2.34 per 1000 person-months (95%CI 1.49 to 3.66).

Patients with prior history of atrial fibrillation had a mortality rate which was 15.12 per 1000 person-months (95%CI 14.75 to 15.51). This was higher than that of patients without prior history of atrial fibrillation, who had a mortality rate of 13.21 per 1000 person-months (95%CI 12.95 to 13.47).

Patients with prior history of anaemia had a mortality rate which was 19.47 per 1000 person-months (95%CI 18.87 to 20.10). This was higher than that of patients without prior history of anaemia, who had a mortality rate of 12.75 per 1000 person-months (95%CI 12.53 to 12.97).

Patients with prior history of cardiomyopathy had a mortality rate which was 5.84 per 1000 person-months (95%CI 5.20 to 6.56). This was lower than that of patients without prior history of cardiomyopathy, who had a mortality rate of 14.22 per 1000 person-months (95%CI 14.00 to 14.44).

Patients with prior history of cerebrovascular disease had a mortality rate which was 19.11 per 1000 person-months (95%CI 18.26 to 20.00). This was higher than that of patients without prior history of cerebrovascular disease, who had a mortality rate of 13.40 per 1000 person-months (95%CI 13.18 to 13.62).

Patients with prior history of coronary heart disease had a mortality rate which was 11.01 per 1000 person-months (95%CI 10.62 to 11.41). This was lower than

that of patients without prior history of coronary heart disease, who had a mortality rate of 14.71 per 1000 person-months (95%CI 14.47 to 14.96).

Patients with prior history of chronic kidney disease had a mortality rate which was 18.90 per 1000 person-months (95%CI 18.41 to 19.40). This was higher than that of patients without prior history of chronic kidney disease, who had a mortality rate of 12.23 per 1000 person-months (95%CI 12.00 to 12.46).

Patients with prior history of chronic obstructive pulmonary disease had a mortality rate which was 15.28 per 1000 person-months (95%CI 14.33 to 16.29). This was higher than that of patients without prior history of chronic obstructive pulmonary disease, who had a mortality rate of 13.79 per 1000 person-months (95%CI 13.58 to 14.01).

Patients with prior history of cancer had a mortality rate which was 13.76 per 1000 person-months (95%CI 13.55 to 13.98). This was lower than that of patients without prior history of cancer, who had a mortality rate of 20.86 per 1000 person-months (95%CI 18.85 to 23.09).

Patients with prior history of dyspnoea had a mortality rate which was 15.66 per 1000 person-months (95%CI 14.84 to 16.52). This was higher than that of patients without prior history of dyspnoea, who had a mortality rate of 13.73 per 1000 person-months (95%CI 13.51 to 13.95).

Patients with prior history of hypercholesterolaemia had a mortality rate which was 12.15 per 1000 person-months (95%CI 11.55 to 12.78). This was lower than that of patients without prior history of hypercholesterolaemia, who had a mortality rate of 14.07 per 1000 person-months (95%CI 13.85 to 14.30).

Patients with prior history of hypertension had a mortality rate which was 14.46 per 1000 person-months (95%CI 14.14 to 14.79). This was higher than that of patients without prior history of hypertension, who had a mortality rate of 13.39 per 1000 person-months (95%CI 13.12 to 13.68).

Patients with prior history of left ventricular hypertrophy had a mortality rate which was 11.54 per 1000 person-months (95%CI 10.32 to 12.91). This was

lower than that of patients without prior history of left ventricular hypertrophy, who had a mortality rate of 13.92 per 1000 person-months (95%CI 13.71 to 14.14).

Patients with prior history of pulmonary congestion had a mortality rate which was 20.28 per 1000 person-months (95%CI 14.63 to 28.11). This was higher than that of patients without prior history of pulmonary congestion, who had a mortality rate of 13.86 per 1000 person-months (95%CI 13.65 to 14.07).

Patients with prior history of smoking had a mortality rate which was 12.56 per 1000 person-months (95%CI 12.32 to 12.80). This was lower than that of patients without prior history of smoking, who had a mortality rate of 17.30 per 1000 person-months (95%CI 16.86 to 17.76).

Patients with prior history of diabetes mellitus had a mortality rate which was 14.33 per 1000 person-months (95%CI 13.87 to 14.80). This was higher than that of patients without prior history of diabetes mellitus, who had a mortality rate of 13.75 per 1000 person-months (95%CI 13.87 to 14.80).

4.1.2 Graphs

Kaplan-Meier graphs observing the cumulative probabilities of survival in different exposure groups were completed whilst also taking note of significant differences between sub-exposure groups. A median survival time could not be reported due to all exposure groups having less than 50% mortality during the follow up period. p-values were calculated for mean survival time using the log rank test and the long rank test for trend for ordered categorical variables.

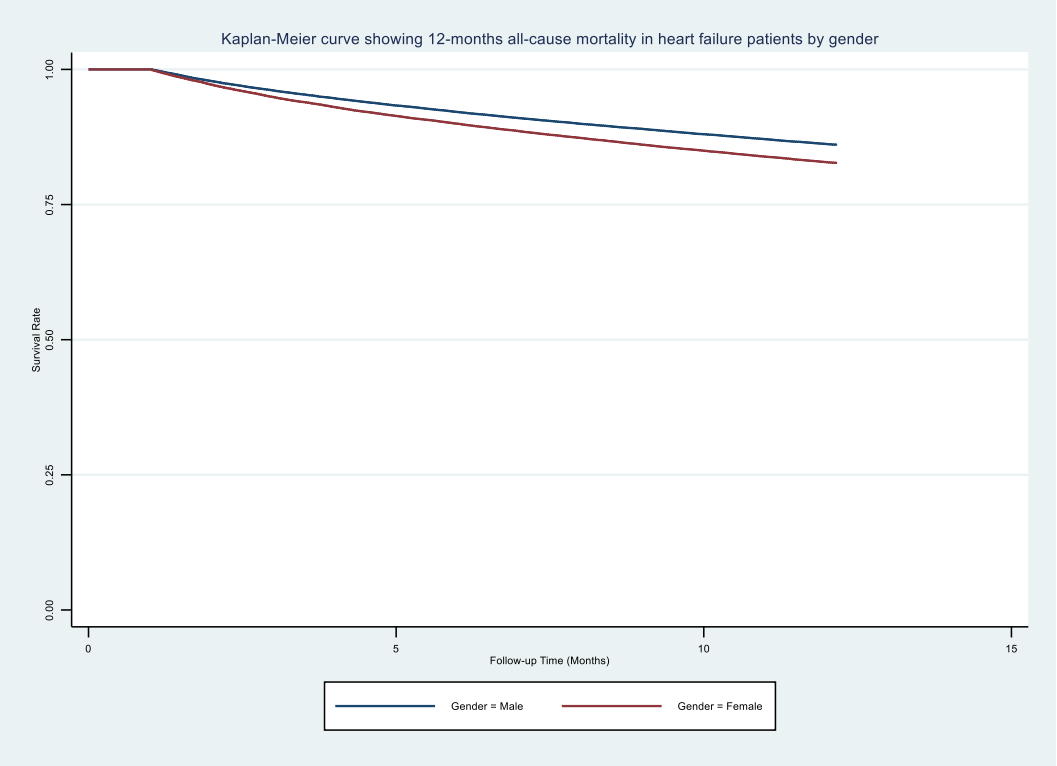


Figure 9- Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by gender, p <0.0001

Regarding gender (Figure 9), females had a lower survival rate throughout the follow up period. This was statistically significant (p<0.0001).

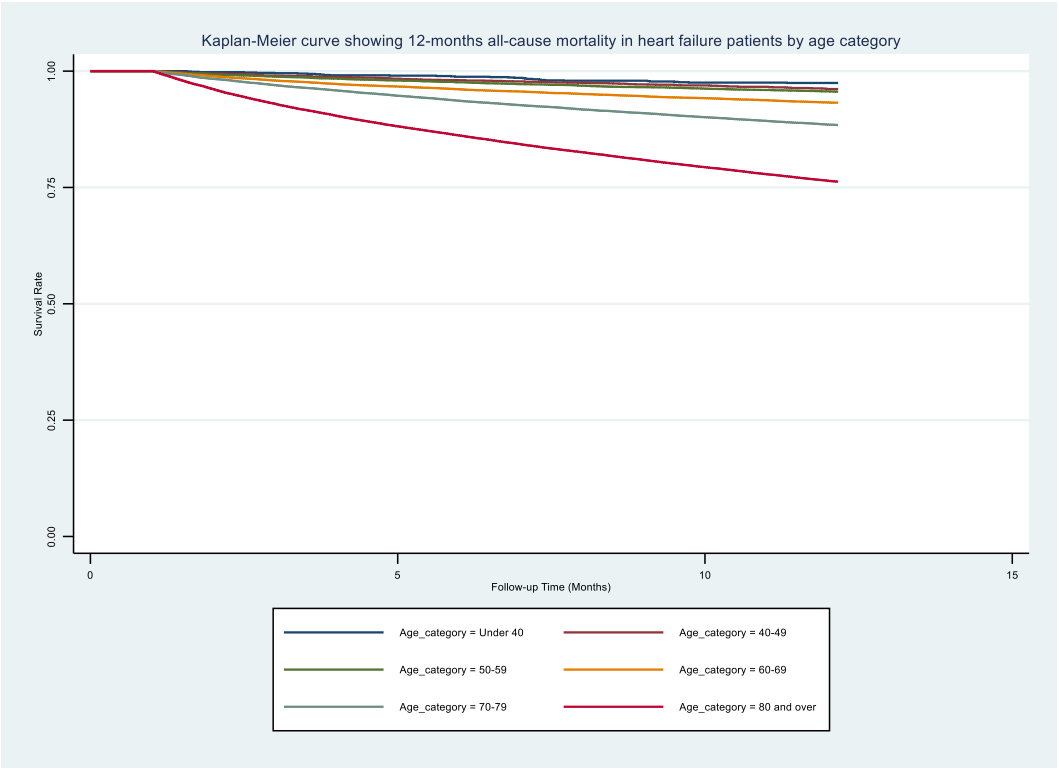


Figure 10-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by age category, p<0.0001

With age category (Figure 10), there was a trend of survival rates being decreasing with age throughout the follow up period. This trend was statistically significant (p<0.0001).

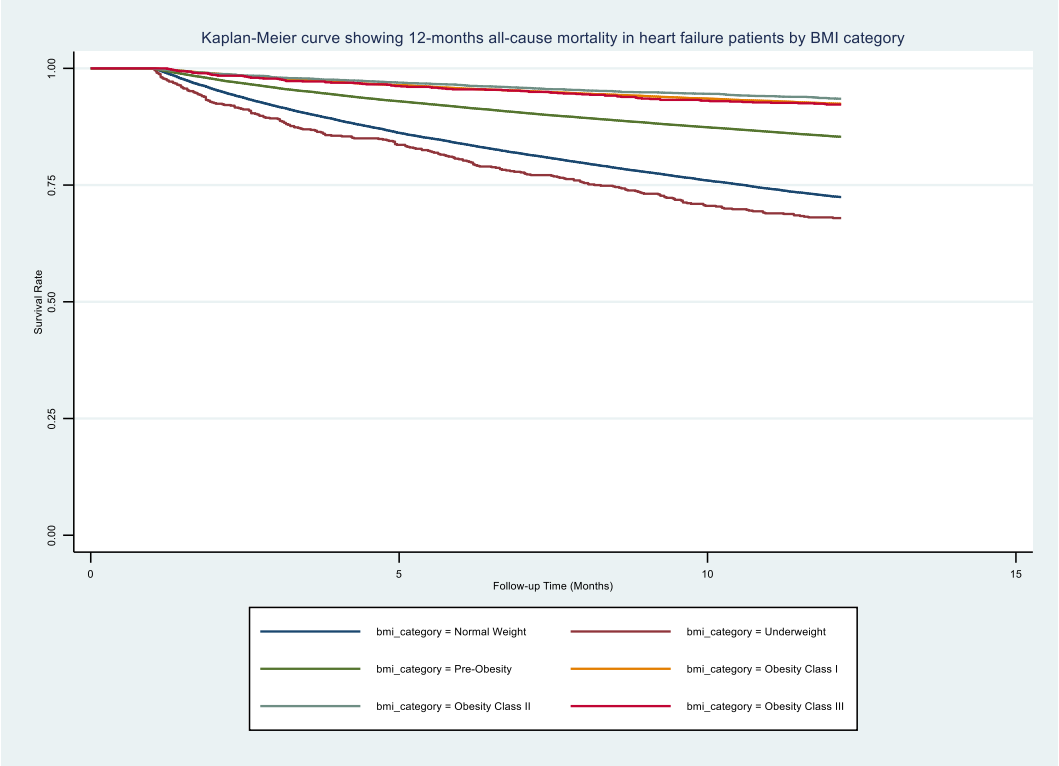


Figure 11- Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by BMI category, p<0.0001

With BMI category (Figure 11), underweight patients had the lowest survival rate. This was followed by patients of normal weight. Patients classed as being in pre-obesity had the third lowest survival rate and patients classed as obesity class 3 followed. Patients classed as obesity class 2 had the highest survival rate. This trend was statistically significant (p<0.0001).

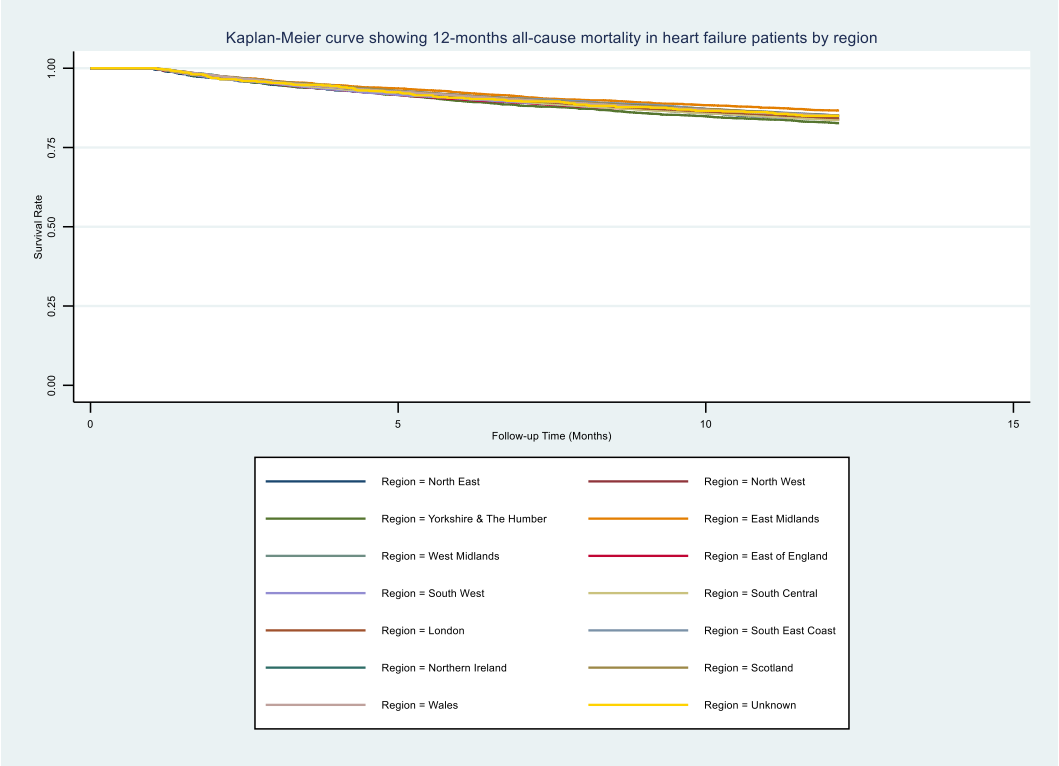


Figure 12-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by region, p<0.0001

With region (Figure 12), survival rates did not show a consistent pattern throughout the period of follow up. Despite this, there was a significant difference between the different regions (p<0.0001)

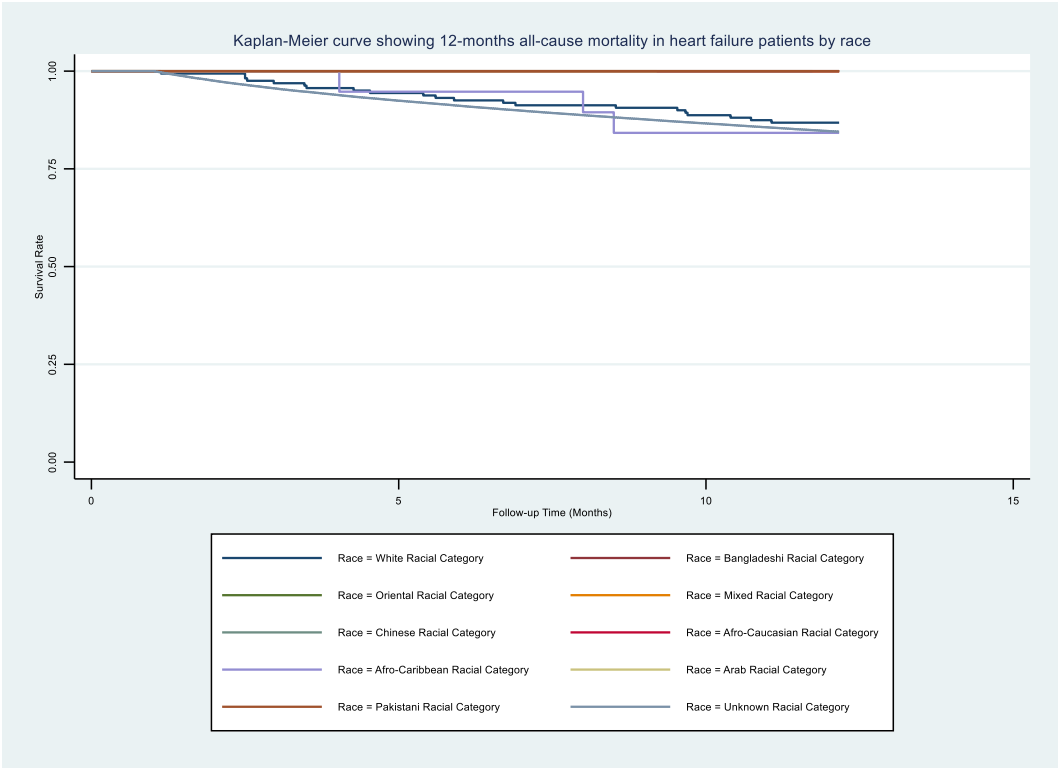


Figure 13-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by race, p=0.9808

With regards to race (Figure 13), survival rates did not show a consistent pattern throughout the period of follow up and only 3 races registered deaths. There was not a significant difference between the different races (p= 0.9808)

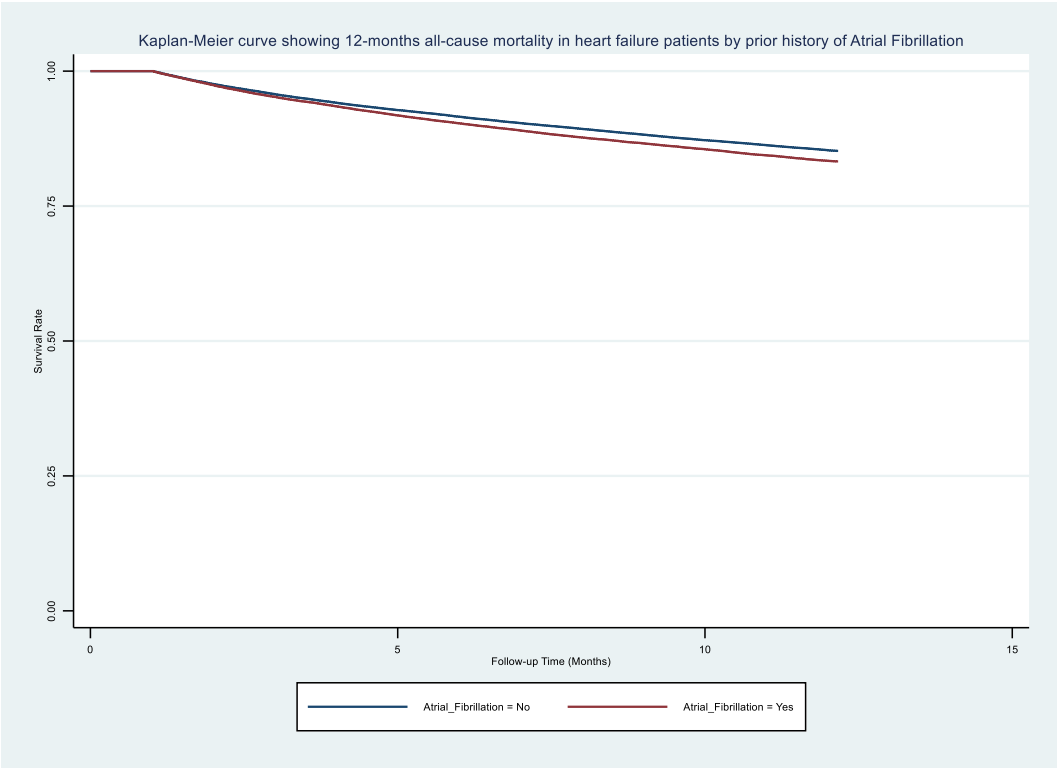


Figure 14-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Atrial Fibrillation, p<0.0001

Patients who had previously had atrial fibrillation had a lower survival rate throughout the follow up period compared to patients who did not (Figure 14). This was statistically significant (p<0.0001).

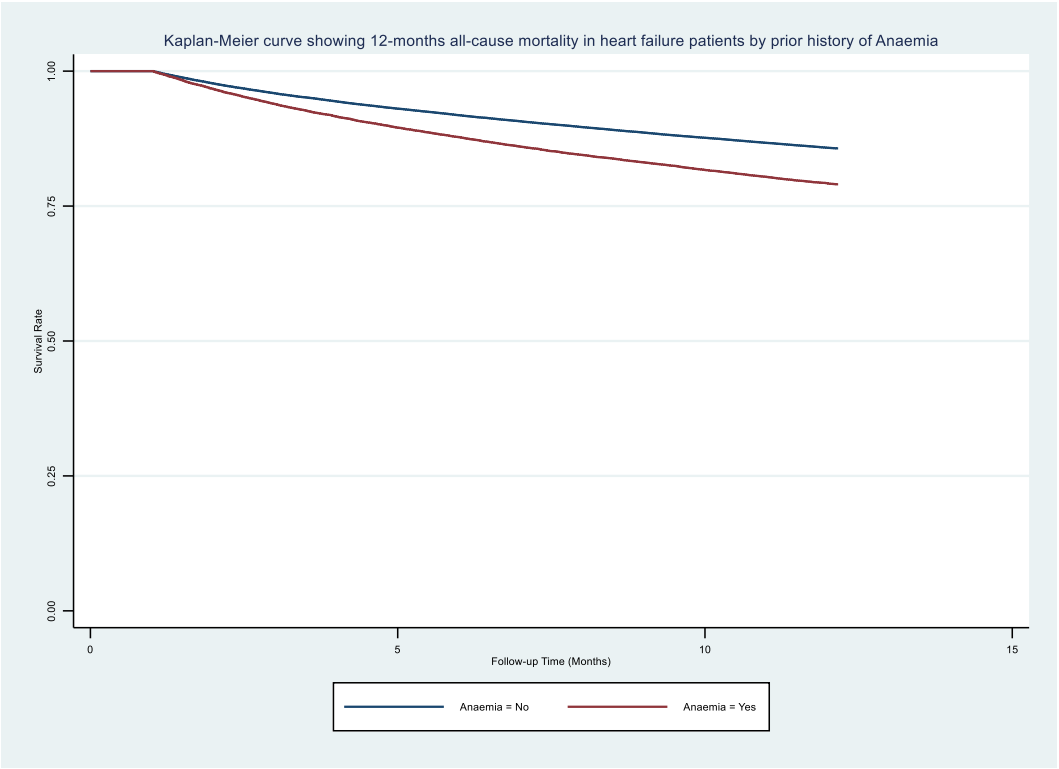


Figure 15-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Anaemia, p<0.0001

Patients who had previously had anaemia had a lower survival rate throughout the follow up period when compared to patients who did not have anaemia (Figure 15). This was statistically significant (p<0.0001).

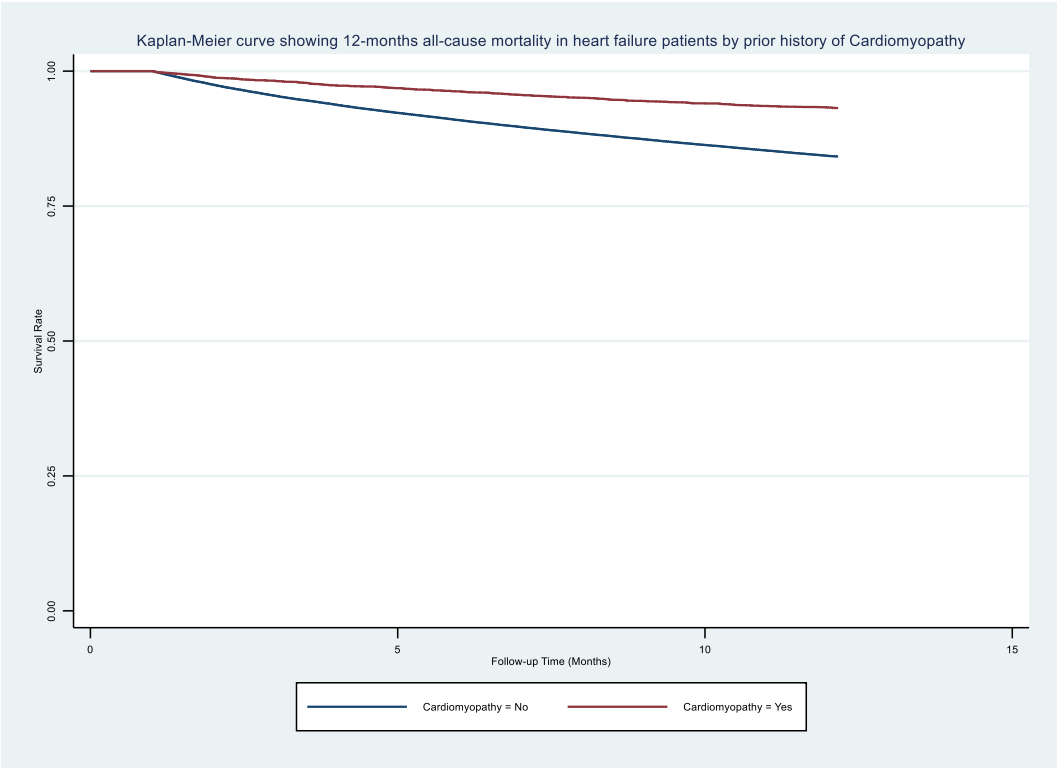


Figure 16- Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Cardiomyopathy, p<0.0001

Patients who previously had cardiomyopathy had a higher survival rate throughout the follow up period compared to patients who did not (Figure 16) This was statistically significant (p<0.0001).

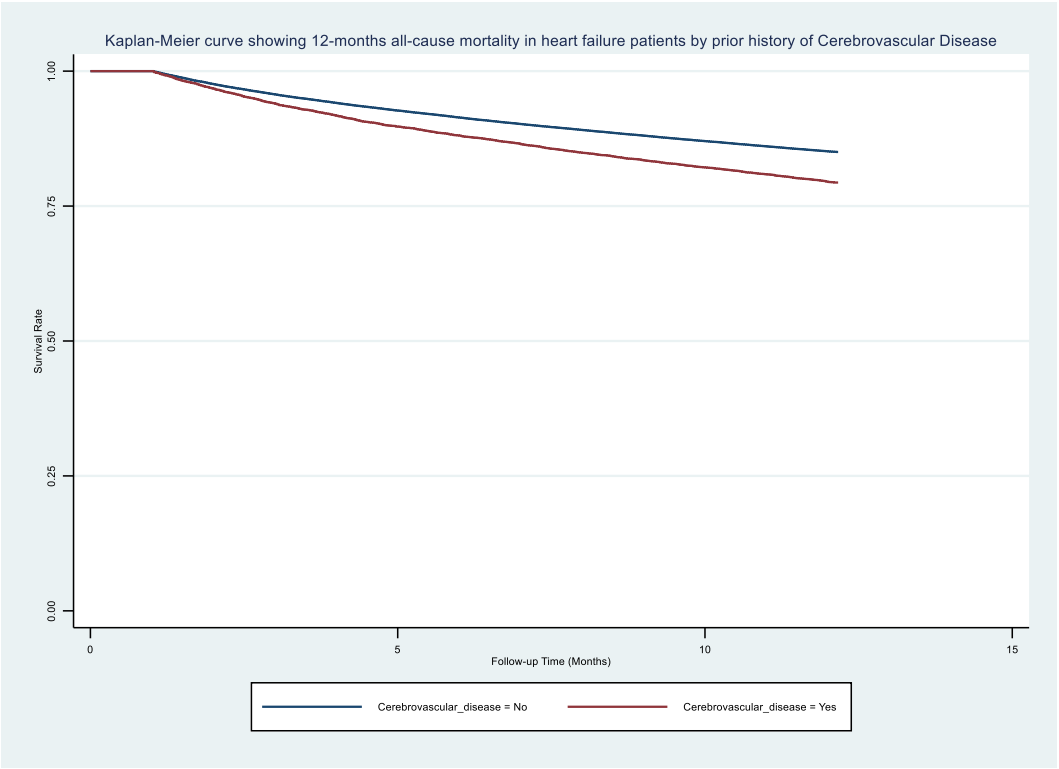


Figure 17-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by Cerebrovascular Disease, p<0.0001

Patients who had previously had cerebrovascular disease had a lower survival rate throughout the follow up period compared to patients who did not (Figure 17) This was statistically significant (p<0.0001).

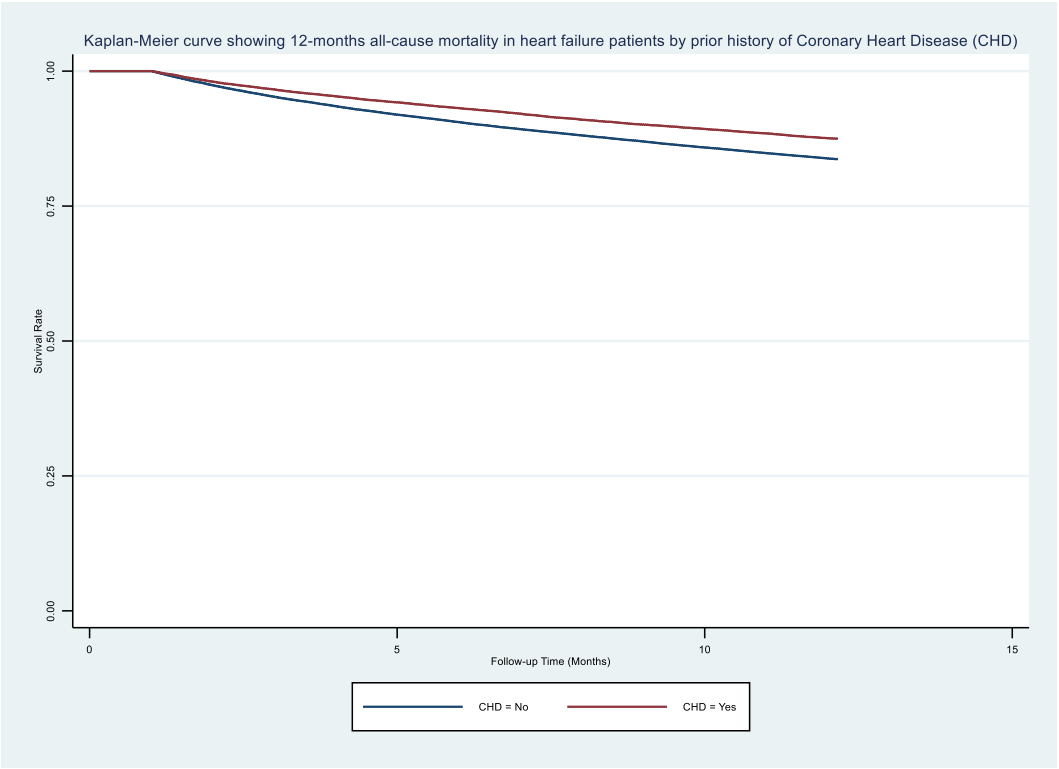


Figure 18- Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by Coronary Heart Disease, p<0.0001

Patients who had previously had coronary heart disease had a higher survival rate throughout the follow up period compared to patients who did not (Figure 18). This was statistically significant (p<0.0001).

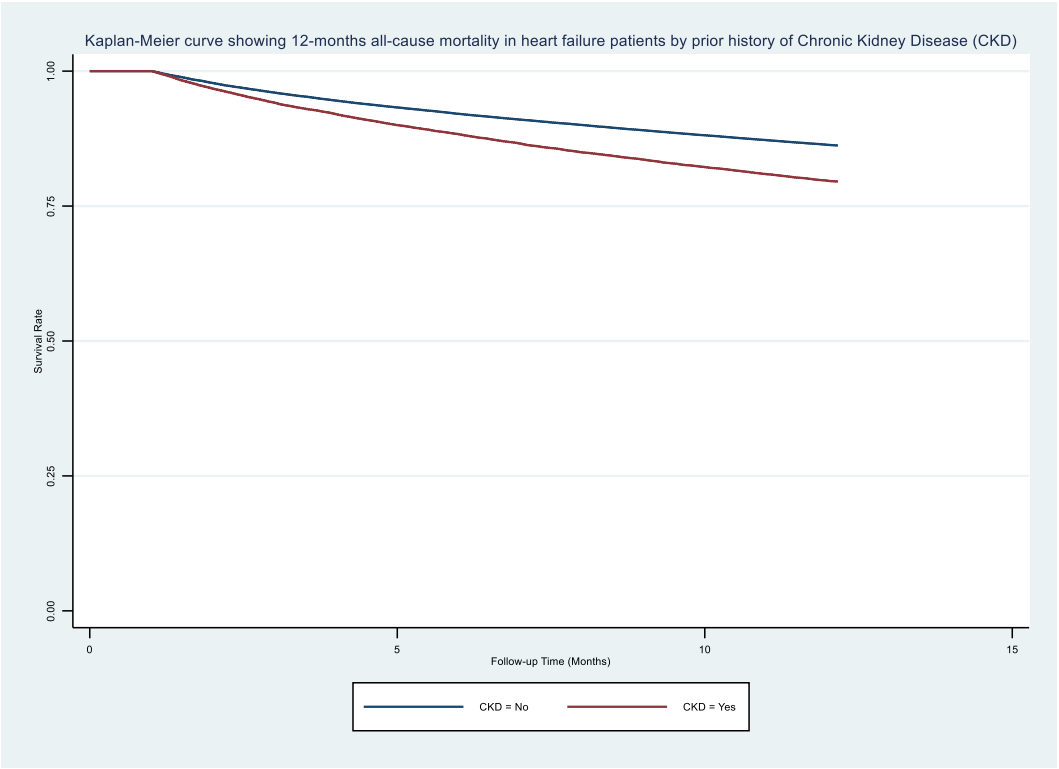


Figure 19- Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by Chronic Kidney Disease, p<0.0001

Patients who had previously had chronic kidney disease had a lower survival rate throughout the follow up period compared to patients who did not have prior history of chronic kidney disease (Figure 19). This was statistically significant (p<0.0001).

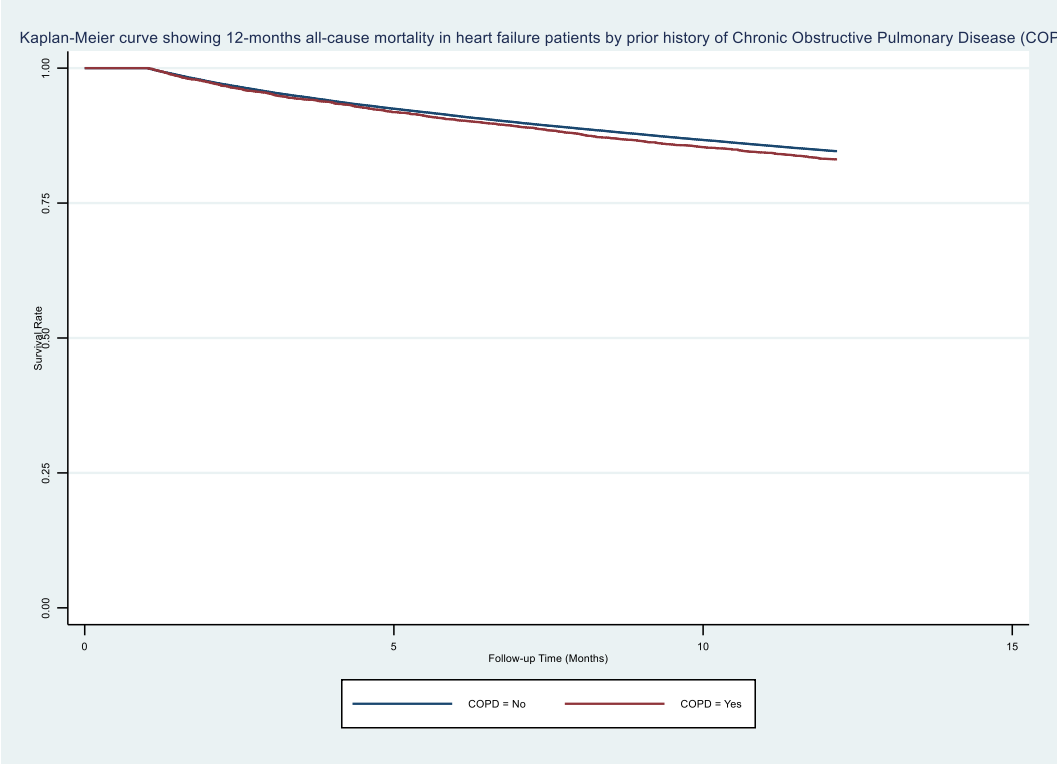


Figure 20- Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by Chronic Obstructive Pulmonary Disease (COPD), p<0.0001

Patients who had previously had chronic obstructive pulmonary disease had a lower survival rate throughout the follow up compared to patients who did (Figure 20). This was statistically significant (p<0.0001).

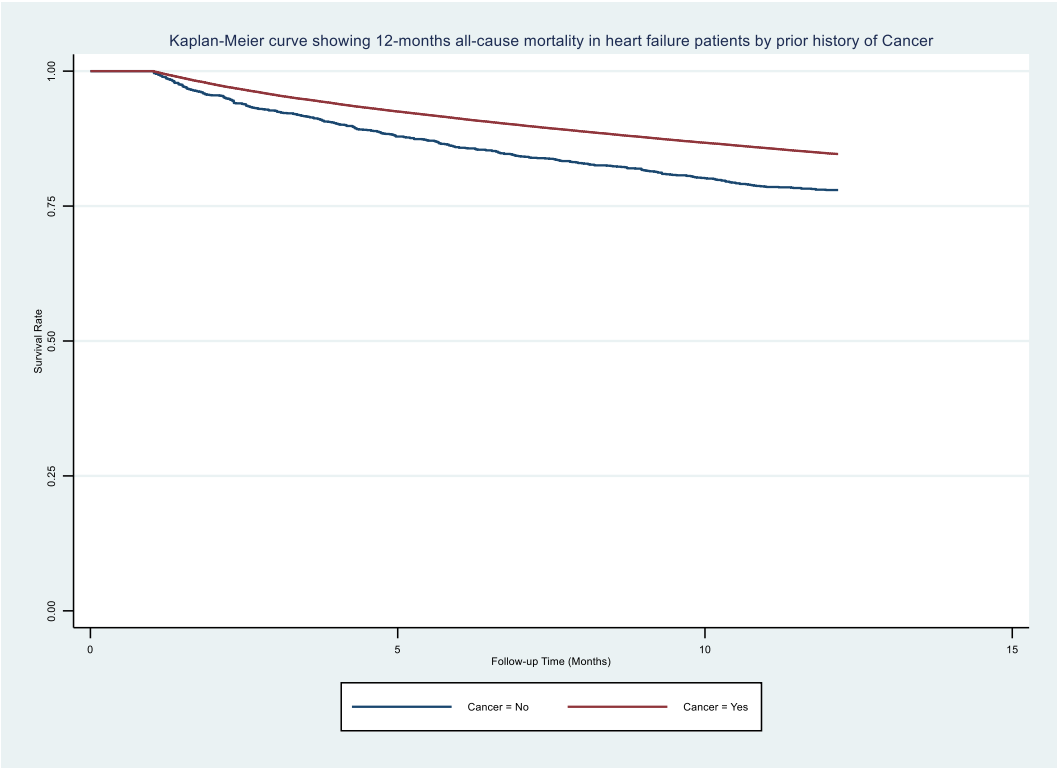


Figure 21-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Cancer, p<0.0001

Patients who had a prior history of cancer had a higher survival rate throughout the follow up period compared to patients who did not have prior history of cancer (Figure 21) This was statistically significant (p<0.0001).

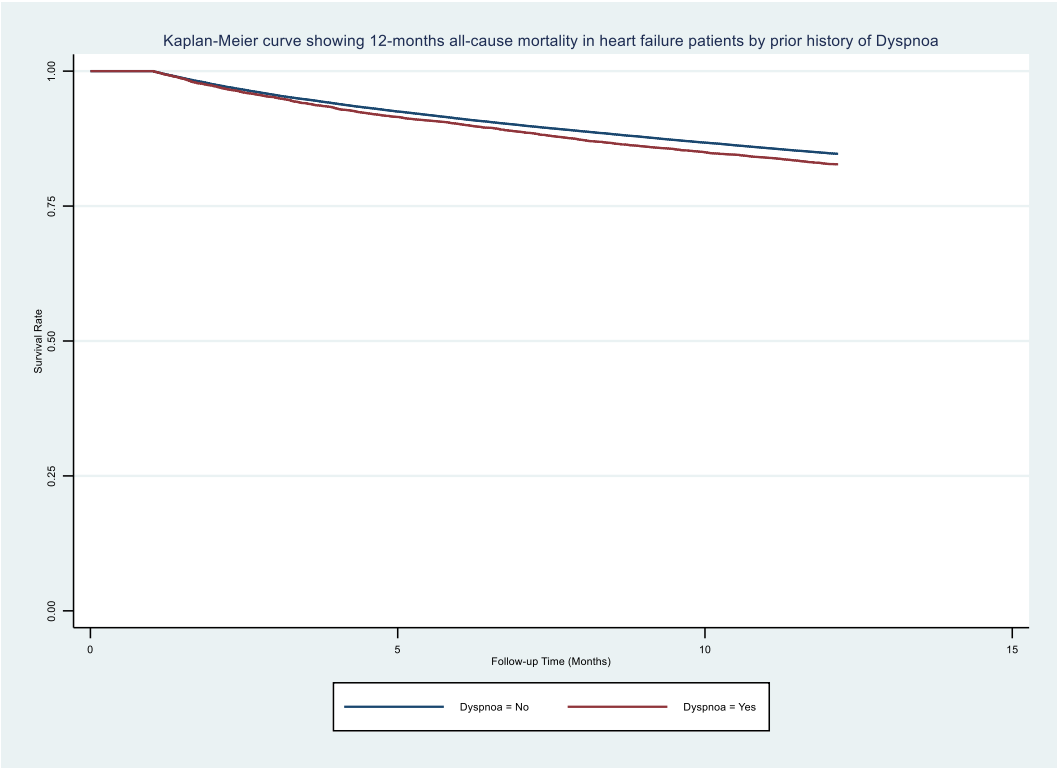


Figure 22-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Dyspnoea, p<0.0001

Patients who had previously had dyspnea had a lower survival rate throughout the follow up period compared to patients who did not have prior history of dyspnea (Figure 22). This was statistically significant (p<0.0001).

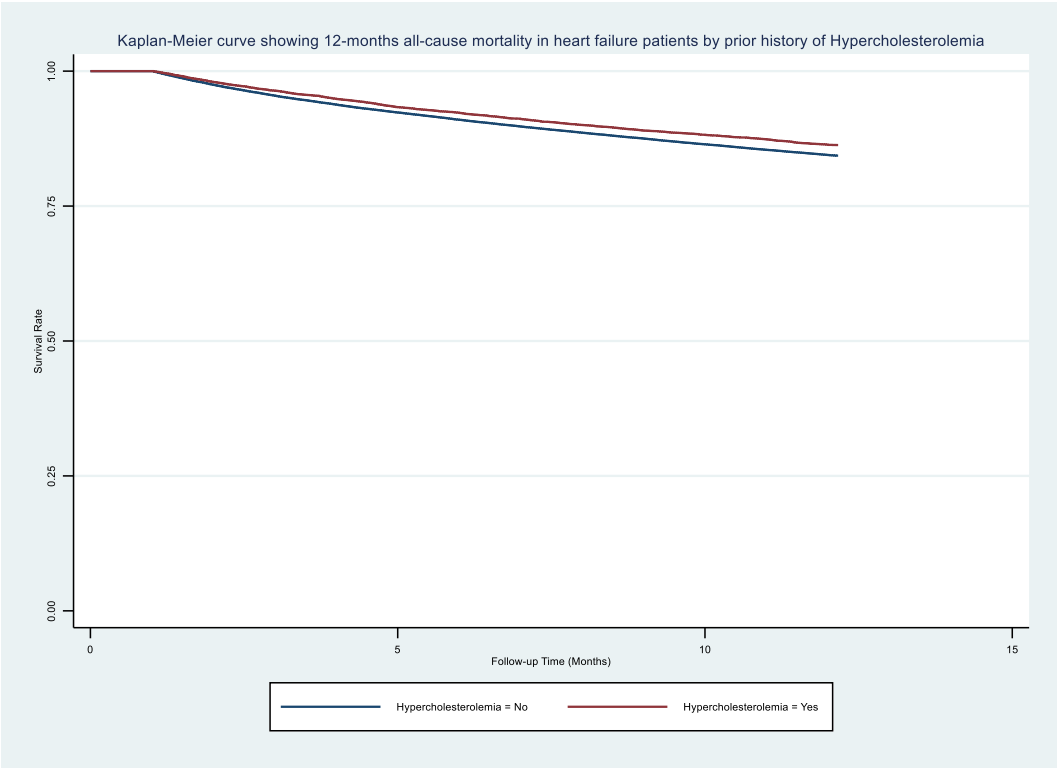


Figure 23-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Hypercholesterolaemia, p<0.0001

Patients who had previously had hypercholesterolemia had a higher survival rate throughout the follow up compared to patients who did not have prior history of hypercholesterolemia (Figure 23). This was statistically significant (p< p<0.0001).

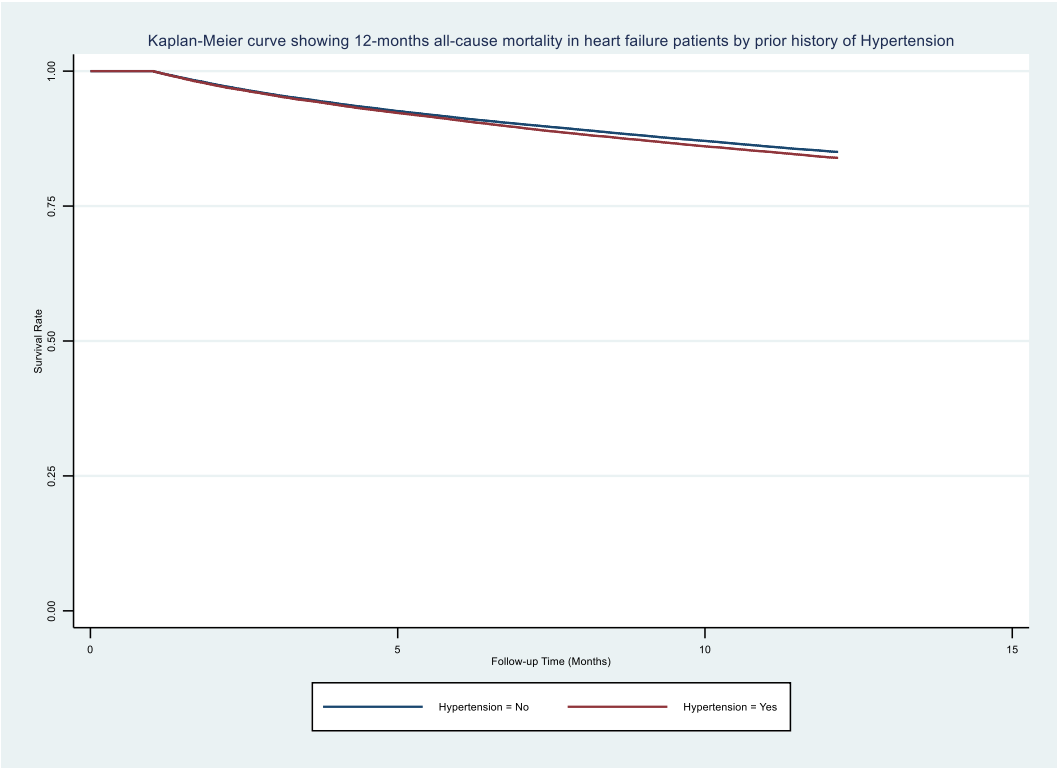


Figure 24-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Hypertension, p<0.0001

Patients who had previously had hypertension had a lower survival rate throughout the follow up period compared to patients who did not have prior history of hypertension (Figure 24). This was statistically significant (p<0.0001).

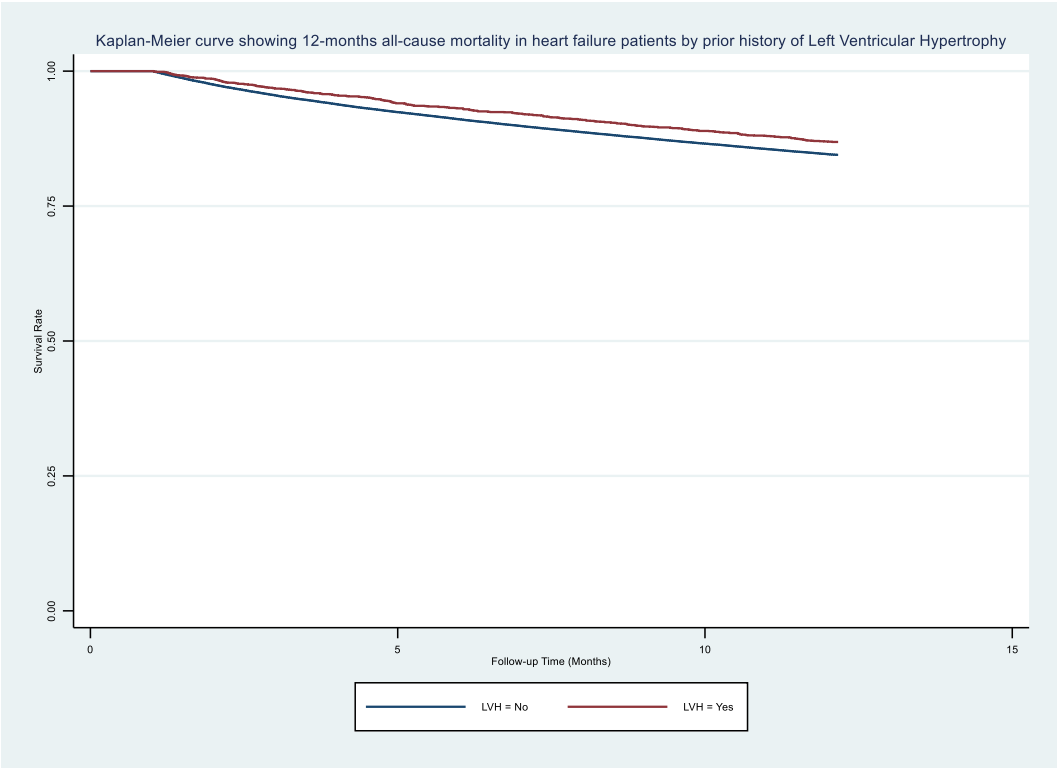


Figure 25-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Left Ventricular Hypertrophy, p=0.0012

Patients who had previously left ventricular hypertrophy had a higher survival rate throughout the follow up period compared to patients who did not have prior history of left ventricular hypertrophy (Figure 25). This was statistically significant (p=0.0012).

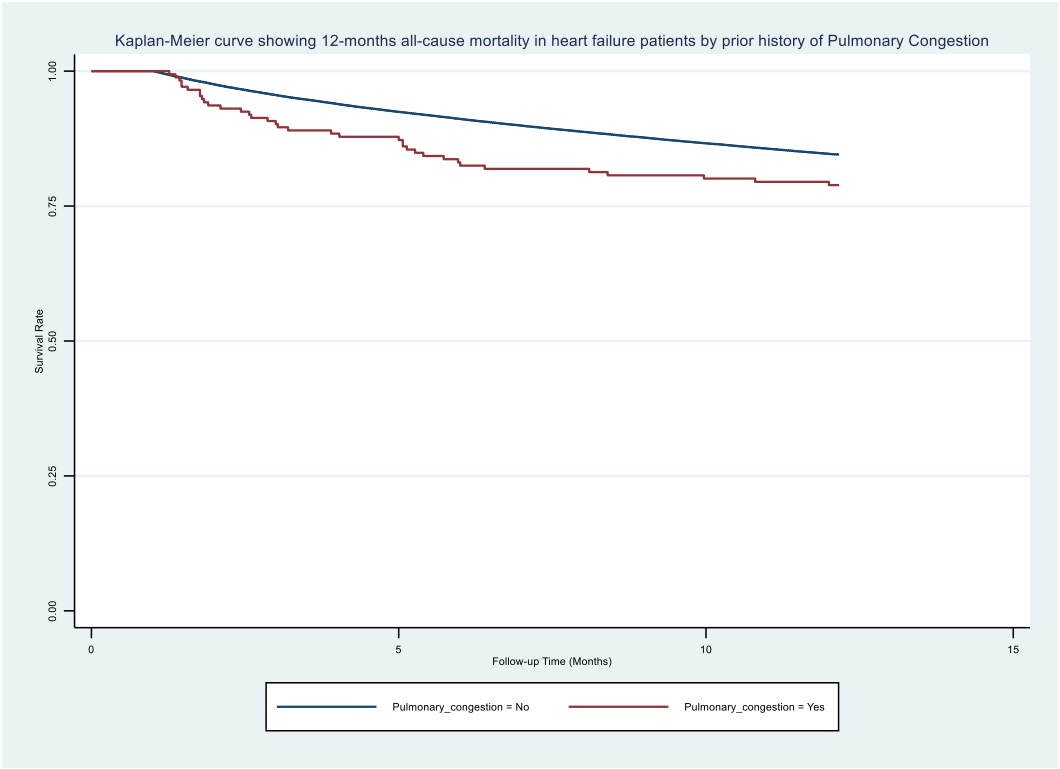


Figure 26-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Pulmonary Congestion, p=0.0217

Survival did not differ significantly between those with or without a history of pulmonary congestion (p=0.0217, Figure 26)

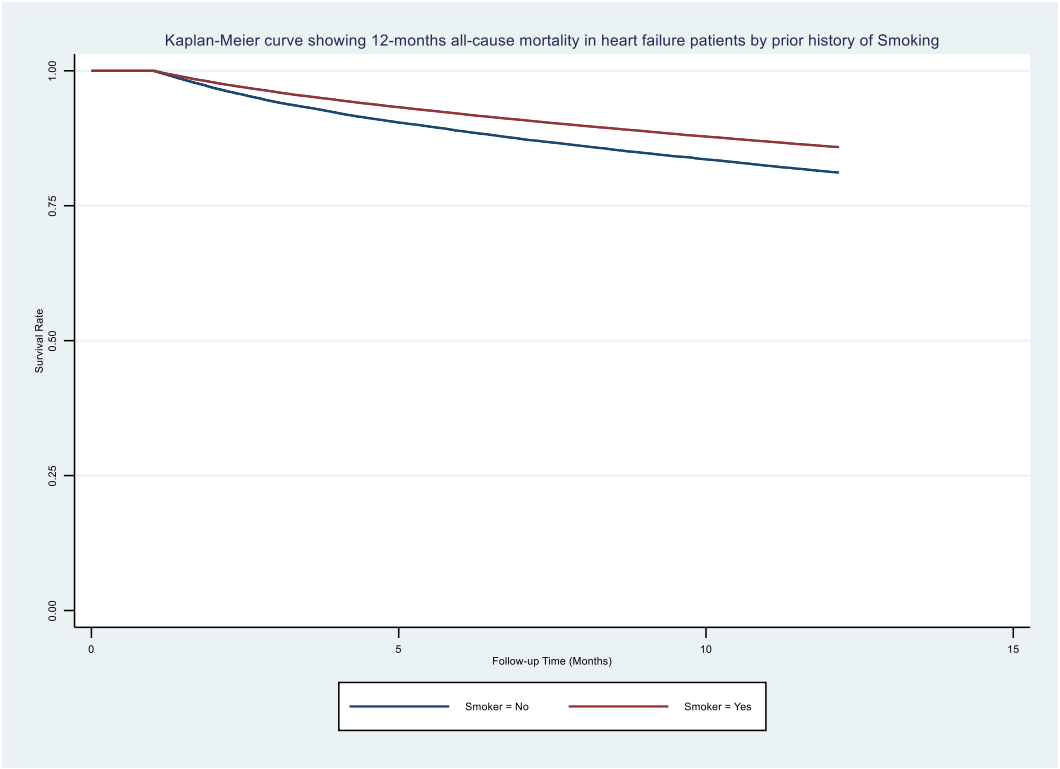


Figure 27-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Smoking, p<0.0001

Patients who had previously smoked had a higher survival rate throughout the follow up period compared patients who did not have prior history of smoking (Figure 27). This was statistically significant (p<0.0001).

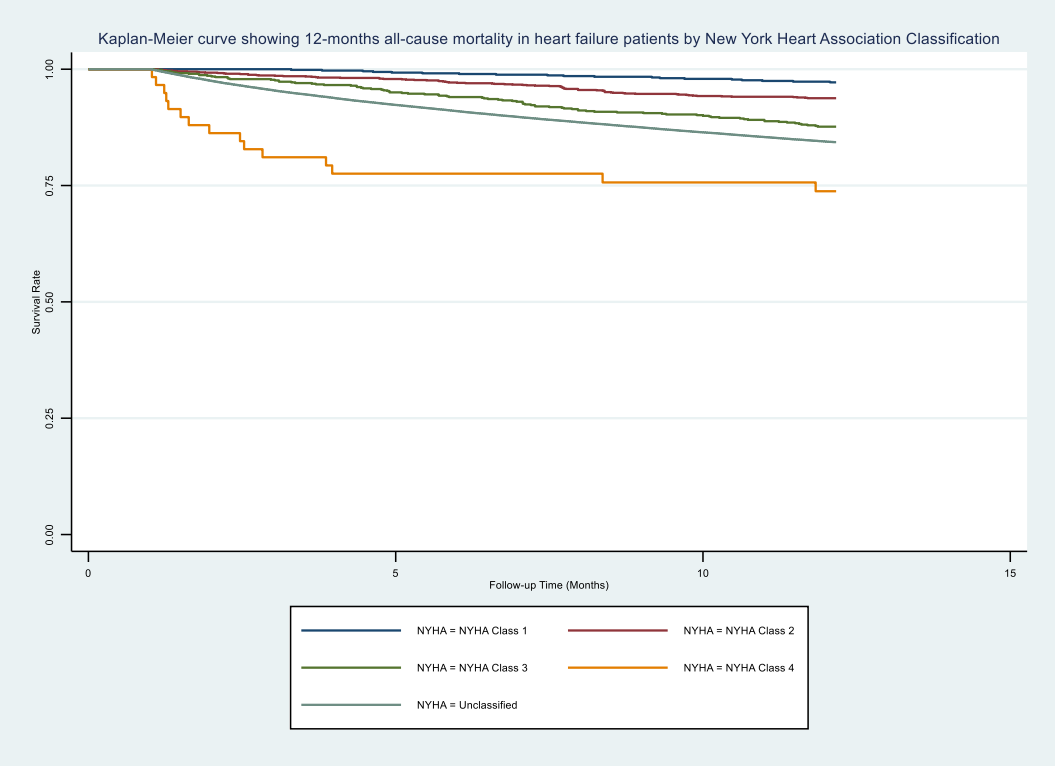


Figure 28-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by New York Heart Association Classification, p<0.0001

With NYHA Classification (Figure 28), NYHA class a decreases survival rate throughout the follow up period. This trend was statistically significant (p<0.0001).

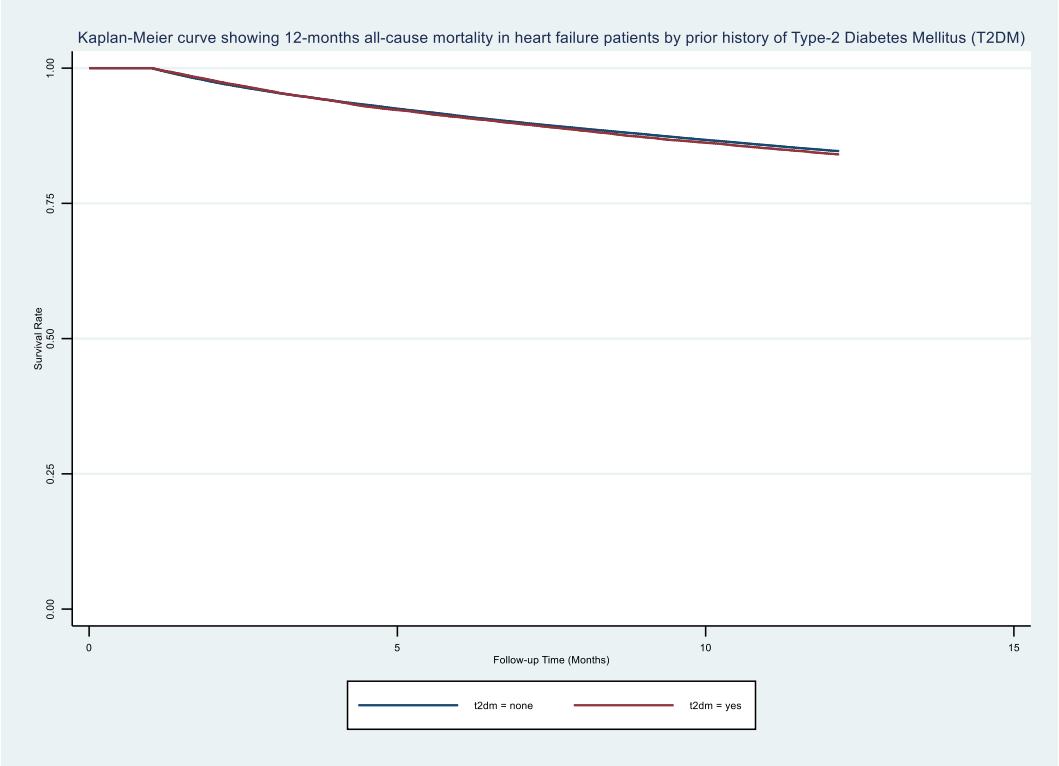


Figure 29-Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by prior history of Type-2 Diabetes Mellitus(T2DM), p=0.0290

Survival did not differ significantly between those with or without a history of type 2 diabetes (p=0.0290).

4.2 Model Development and Specification

At the completion of the model development and backwards elimination process (Table 2), 8 predictors were removed from the multivariable model. Race was also removed due to incomplete recording and lipid lowering drugs due to collinearity. This left 29 significant predictors for mortality in the final cox-regression model (Table 3). The 10 predictors removed were region, previous history of cardiomyopathy, previous history of COPD, previous history of cancer, previous history of diuretics, hypertension, previous history of left ventricular hypertrophy, total cholesterol, lipid lowering drugs and race.

Exposure	Hazard Ratio(95%CI)	P-value
Gender	1.26 (1.23 to 1.31)	<0.0001

Baseline age	1.06 (1.06 to 1.07)	<0.0001
New York Heart Association Classification		<0.0001
NYHA Class 1 (Ref)		
NYHA Class 2	2.26(1.37 to 3.72)	
NYHA Class 3	4.60 (2.80 to 7.56)	
NYHA Class 4	11.76 (5.97 to 23.13)	
Unclassified	6.00 (3.83 to 9.42)	
BMI Category		<0.0001
Normal Weight (Ref)		
Underweight	1.22(1.07 to 1.39)	
Pre-Obesity	0.49(0.48 to 0.51)	
Obesity Class I	0.24(0.23 to 0.26)	
Obesity Class II	0.21(0.18 to 0.24)	
Obesity Class III	0.25(0.20 to 0.31)	
Race		0.1136
White (ref)		
Afro-Caribbean Racial Category	1.21(0.36 to 4.06)	
Region		<0.0001
North West	0.91(0.79 to 1.05)	
Yorkshire & The Humber	1.08(0.92 to 1.25)	
East Midlands	0.81(0.69 to 0.95)	
West Midlands	0.97(0.84 to 1.12)	
East of England	1.00(0.86 to 1.16)	
South West	1.00(0.87 to 1.16)	

South Central	1.00(0.87 to 1.16)	
London	0.96(0.84 to 1.11)	
South East Coast	0.91(0.79 to 1.05)	
Northern Ireland	0.92(0.79 to 1.08)	
Scotland	0.92(0.80 to 1.05)	
Wales	0.92(0.80 to 1.06)	
Prior use of ACE inhibitors	0.71 (0.65 to 0.78)	<0.0001
Prior use of beta-blockers	0.65 (0.63 to 0.68)	<0.0001
Prior use of digoxin	1.31(1.26 to 1.35)	<0.0001
Prior use of statins	0.31 (0.23 to 0.42)	<0.0001
Prior use of lipid lowering drugs	0.71(0.65 to 0.78)	<0.0001
Prior History of Atrial fibrillation	1.44 (1.11 to 1.18)	<0.0001
Prior history of Alcohol Abuse	0.73(0.68 to 0.80)	<0.0001
Prior history of Anemia	1.52(1.47 to 1.58)	<0.0001
Prior history of Left Ventricular Hypertrophy	0.83(0.74 to 0.93)	0.0008
Prior history of Cancer	0.66(0.60 to 0.73)	<0.0001
Prior history of Cardiomyopathy	0.41(0.37 to 0.46)	<0.0001
Prior history of Cerebrovascular Disease	1.42(1.36 to 1.49)	<0.0001
Prior history of coronary heart disease	0.75(0.72 to 0.78)	<0.0001
Prior history of chronic kidney disease	1.54(1.49 to 1.59)	<0.0001
Prior history of chronic obstructive pulmonary disease	1.11 (1.04 to 1.18)	0.0030

Prior history of Diuretics	1.45(1.39 to 1.51)	<0.0001
Prior history of Dyspnoea	1.14(1.08 to 1.21)	<0.0001
Prior history of Hypercholesterolemia	0.86(0.82 to 0.91)	<0.0001
Prior history of Hypertension	1.07(1.05 to 1.11)	<0.0001
Prior history of Pulmonary congestion	1.46(1.05 to 2.03)	0.0319
Prior history of Smoking	0.78(0.76 to 0.81)	<0.0001
Prior history of Type-2 diabetes mellitus	1.04(1.00 to 1.08)	0.0297
Albumin concentration (mg/dL)	0.90 (0.90 to 0.91)	<0.0001
Bilirubin concentration(mg/L)	1.00(1.00 to 1.01)	<0.0006
Systolic blood pressure(mmHg)	0.99(0.99 to 0.99)	<0.0001
HDL cholesterol value (mg/dL)	1.22(1.18 to 1.26)	<0.0001
LDL cholesterol value (mg/dL)	0.90(0.89 to 0.92)	<0.0001
VLDL cholesterol value (mg/dL)	2.07 (2.01 to 2.14)	<0.0001
Creatinine value (mg/dL)	1.00(1.00 to 1.01)	<0.0001
CRP value (mg/dL)	1.02 (1.02 to 1.02)	<0.0001
GFR value (mL/min)	0.98(0.98 to 0.98)	<0.0001
JVP(SD) (cm)	0.93 (0.92 to 0.94)	<0.0001

Table 2 - Univariate unadjusted hazard risks for candidate predictors

Exposure	Hazard Ratio(95%CI)
Gender	1.30 (1.25 to 1.36)
Baseline age	1.06 (1.05 to 1.07)
New York Heart Association Classification	

NYHA Class 1 (Ref)	
NYHA Class 2	1.59(0.96 to 2.62)
NYHA Class 3	2.53 (1.54 to 4.17)
NYHA Class 4	8.13 (4.13 to 16.00)
Unclassified	3.10 (1.98 to 4.86)
BMI Category	
Normal Weight (Ref)	
Underweight	0.63(0.54 to 0.73)
Pre-Obesity	0.92(0.87 to 0.98)
Obesity Class I	0.83(0.75 to 0.93)
Obesity Class II	1.25(1.03 to 1.51)
Obesity Class III	3.32(2.47 to 4.48)
Prior use of ACE inhibitors	1.26 (1.15 to 1.38)
Prior use of beta-blockers	0.95 (0.92 to 0.98)
Prior use of digoxin	0.94(0.90 to 0.98)
Prior use of statins	0.46 (0.34 to 0.62)
Prior History of Atrial fibrillation	0.94 (0.90 to 0.97)
Prior history of Alcohol Abuse	1.19(1.10 to 1.30)
Prior history of Anemia	1.33(1.28 to 1.38)
Prior history of Cerebrovascular Disease	1.46(1.39 to 1.53)

Prior history of coronary heart disease	0.90(0.86 to 0.94)
Prior history of chronic kidney disease	0.81(0.77 to 0.84)
Prior history of Dyspnoea	1.39(1.31 to 1.46)
Prior history of Hypercholesterolemia	1.49(1.41 to 1.58)
Prior history of Hypertension	1.21(1.17 to 1.25)
Prior history of Pulmonary congestion	1.86(1.33 to 2.60)
Prior history of Smoking	0.78(0.76 to 0.81)
Prior history of Type-2 diabetes mellitus	0.89(0.85 to 0.93)
Albumin concentration (mg/dL)	0.80 (0.77 to 0.82)
Bilirubin concentration(mg/L)	1.01(1.01 to 1.02)
Systolic blood pressure(mmHg)	1.00(0.99 to 1.00)
LDL cholesterol value (mg/dL)	0.87(0.85 to 0.89)
VLDL cholesterol value (mg/dL)	3.15 (3.05 to 3.25)
Creatinine value (mg/dL)	1.00(1.00 to 1.01)
CRP value (mg/dL)	1.01 (1.01 to 1.01)
GFR value (mL/min)	1.00(0.99 to 1.00)
JVP(SD) (cm)	0.94 (0.93 to 0.96)
Cumulative baseline hazard risk at 12 months	0.17 (0.17 to 0.17)

Table 3 - Fully adjusted multivariate cox-regression model for the prediction of mortality in patients with heart failure

In the final multivariable analyses with the predictors, females were 30% more likely to die within a 12-month period after diagnosis with Heart Failure, when compared to males (95%CI 1.25 to 1.36). In addition to this, for every yearly

increase in age, there is a 6% increased risk of all-cause mortality within a year (95% CI 1.05 to 1.07).

New York Heart Association Classification was significantly associated with 12-month all-cause mortality. When compared to patients with an NYHA Classification of 1, patients with an NYHA Classification of 2 had a 59% increased risk of all-cause mortality (95%CI 0.96 to 2.62) whilst patients with an NYHA Classification of 2 had around a 2.5 times increased risk (95%1.54 to 4.17). Patients with an NYHA Class of 4 had around an 8 times increased risk (95%CI 4.13 to 16.00).

BMI category was significantly associated with 12-month all-cause mortality. When compared to patients with a normal BMI, underweight patients had a 37% decreased risk of all-cause mortality (95%CI 0.75 to 0.93) whilst patients classed as Obesity Class I had around a 17% decreased risk (95%CI 0.75 to 0.93). Patients classed as Obesity Class II had around a 25% increased risk (95%1.03 to 1.51) and patients classed as Obesity Class III had around a 3.3 times increased risk (95%CI 2.47 to 4.48). In general, however, there was an 8% reduction in mortality risk for every unit increase in BMI (95%CI 0.91 to 0.93).

Patients who had previously used ACE inhibitors were had a 26% increased risk of all-cause mortality within 12 months (95%CI 1.15 to 1.38) whilst patients who had previously used beta-blockers had a 5% decreased risk of all-cause mortality within 12 months (95%CI 0.92 to 0.98). Patients who had previously used digoxin had a 6% decreased risk of all-cause mortality within 12 months (95%CI 0.90 to 0.98) whilst patients who had previously used statin had a 54% decreased risk of all-cause mortality within 12 months (95%CI 0.34 to 0.62).

Patients with a previous history of atrial fibrillation had a 6% decreased risk of all-cause mortality within 12 months (95%CI 0.90 to 0.97) whilst patients with coronary heart disease had a 10% decreased risk of all-cause mortality (95% CI 0.86 to 0.94). Patients with chronic kidney disease had a 29% decreased risk of all-cause mortality (95% 0.77 to 0.84) whilst patients with type -2 diabetes mellitus were 11% decreased risk (95%CI 0.85 to 0.93). Patients with

cerebrovascular disease had a 46% increased risk of all-cause mortality within a year (95%CI 1.39 to 1.53).

Patients with a previous history of dyspnoea had a 39% increased risk of all-cause mortality within a year of Heart Failure diagnosis (95%CI 1.31 to 1.46) whilst patients with a previous history of pulmonary congestion had an 86% increased risk (95%CI 1.33 to 2.60).

Patients with a previous history of alcohol abuse had a 19% increased of all-cause mortality within a year of Heart Failure diagnosis (95%CI 1.10 to 1.30) whilst patients with a previous history of smoking had a 22% decreased risk (95%CI 0.76 to 0.81).

Patients with a previous history of anaemia had a 33% increased risk of all-cause mortality within a year of diagnosis (95% CI1.28 to 1.38).

Hypertension increased all-cause mortality risk after HF diagnosis by 21% (95%CI 1.17 to 1.25)

Previous history of hypercholesterolemia increases all-cause mortality risk by 49% (95%CI 1.41 to 1.58). Unit increases in VLDL increased mortality risk by around 3.2 per unit increase (95%CI 3.05 to 3.25) whilst Unit increase in LDL results in decreased mortality risk by 13% (95%CI 0.85 to 0.89).

Increases in albumin concentration results in a decrease in risk by 20% (95%CI 0.77 to 0.82).

Every unit increase in bilirubin concentration increases all-cause mortality risk by 1% (95%CI 1.01 to 1.02) whilst every unit increase in creatinine concentration increases all-cause mortality risk by 0.2% (95% CI 0.1% to 0.3% increase). Every unit increase in CRP concentration increases all-cause mortality risk by 1% (95%CI 1.01 to 1.01) whilst every unit increase in GFR decreases all-cause mortality risk by 0.4% (95% CI 0.99 to 1.00).

Every unit decrease in JVP results in a 6% decrease in all-cause mortality risk (95%CI 0.93 to 0.96)

4.2.1 How to use the model

The cox- regression model can be interpreted through the equation $h(t) = h_0(t) \times e^{(\beta 1\ E)} \times e^{(\beta 2\ E)} \times \ldots \times e^{(\beta 29\ E)}$ where h(t) provides the personalised hazard risk at a given point in time t during the follow up period for an individual, $\beta 1$ E provides the hazard ratio for any given predictor $\beta 1$ and $h_0(t)$ provides the baseline hazard risk at time(t) for said individual. Risk prediction for this model in clinical practice may require the use of a computer program, spreadsheet, or web calculator to predict individual risks.

4.3 Model Performance

Model	N	AUC (95%CI)
Final Cox-Regression Model	109,060	0.79 (0.79 to 0.80)
Bootstrap Validation	200	0.79 (0.79 to 0.80)
Difference	200	0.0018 (0.00 to 0.01)
Optimism	200	0.79 (0.79 to 0.80)

Table 4 - Model performance by validation

After adjustment for optimism, the final risk prediction model was able to discriminate patients diagnosed with Heart Failure who had died within 12-months from diagnosis with a C statistic of 0.79 (95% confidence interval 0.79 to 0.80). The agreement between the observed and predicted proportion of events showed excellent apparent calibration. Mean optimism (Shrinkage) was equal to one. (Table 4)

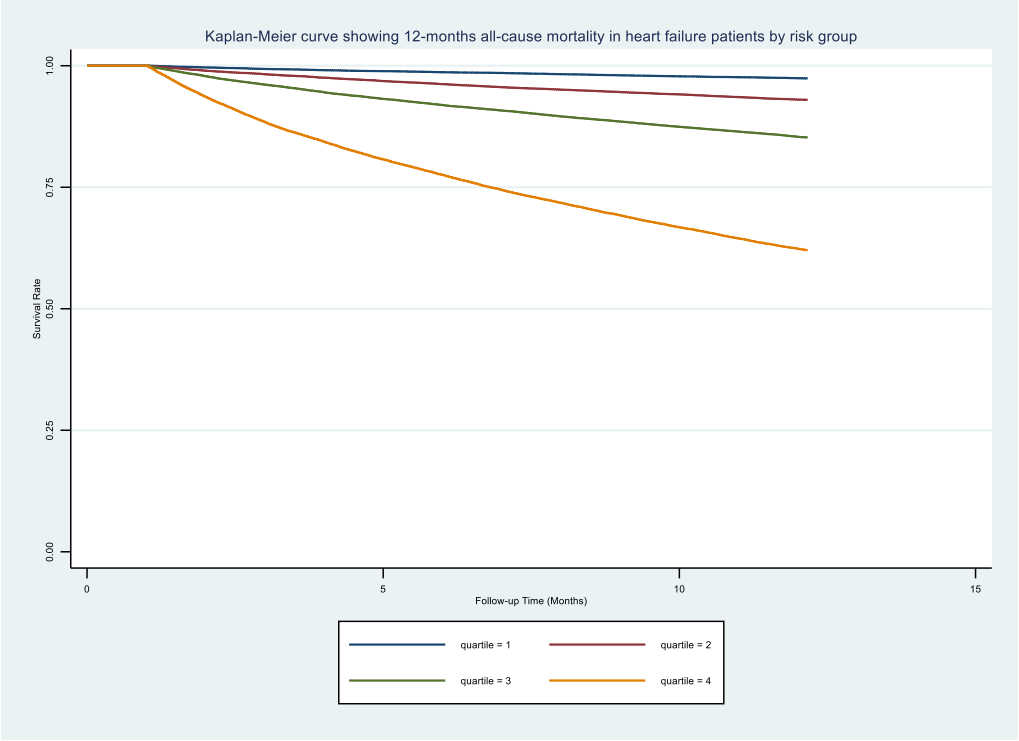


Figure 30- Kaplan-Meier curve showing 12-month mortality in Heart Failure patients by risk group), p<0.0001

With predicted risk groups (figure 30), survival rate decreases with assigned risk quartile throughout the follow up period with the fourth quartile having the lowest survival. This trend was statistically significant (p<0.0001).

Metric	N	Unit (SE)
Discrimination (D)	109,060	1.649 (0.013)

Table 5 - Model performance by discrimination

The D statistic suggests that the prediction model provides a reasonably high amount of prognostic separation (Table 4). Specifically, if one were to form two risk groups of equal size in the validation data, then the corresponding hazard ratio would be $e^{(1.649)} = 5.20$

5 Discussion

5.1 Limitations

With 29 predictors discovered in a cohort of over 100,000 patients from a total of 39 potential predictors, this study is one of the largest cohort studies of individuals with heart failure. As such, its strengths are in its size and study design. In line with the aims of this study we developed a predictive algorithm for HF using multivariable cox regression modelling, validated the model and stratified the model by BMI groupings. Despite this, there were several limitations.

The use of CPRD as a setting for the study was a major strength as it analyses of a large range of predictors that would not otherwise be available in a clinical trial registry. As a result, it was possible to adjust for the largest number of confounders for the relationship between each predictor and mortality which gave novel hazard ratios that, in some cases, challenged current knowledge on these predictors. This was also possible due to the study's inclusion criteria which had little restrictions. Despite this, it must be mentioned, as with most routine databases, there were missing data on some variables recorded in CPRD and multiple imputation had to be completed on patients who had incomplete data on some of these variables. In addition to this there were many predictors and variables that were not recorded at all on CPRD and had to be dropped from the study entirely. This is an important limitation because it means that this model may not be as robust as it could be. Despite this, multiple imputation by chained equations remains a valid and well-known approach to handle data assumed to be missing at random.

Appropriate statistical methods were used throughout the study, which was a strength, as it was possible to see the significance of the differences in baseline characteristics of the two groups being studied as well as their survival distributions for selected predictors. The use of backwards elimination whilst checking for model fit by AIC was an efficient method to test for variable

significance as with 39 predictors a comparable process of forward regression using individual p-values, would have been excessively time consuming.

With regards to the predictors themselves, we did not check for non-linear relationships in risk of mortality or for interactions between common predictors such as gender and age. This would have added an extra sophistication to the model which may have improved accuracy. In addition to this, patients could be further stratified by their heart failure type and ejection fraction, although this is not accurately recorded on CPRD and may need linkage with a separate database. It would also be helpful to stratify predictors such as eGFR, kidney disease and Systolic Blood Pressure as this would have allowed for a better analysis and understanding of their relationship with risk. Many of our biomarkers were found to have modest changes in risk per unit change and it may have been of better utility to have transformed these variables or stratify them to better illustrate their effect.

Validation of the model through AUC by internal validation was an important strength of the study as it evidenced its accuracy, however the lack of external validation is an important limitation of this study as the performance of the model has not been demonstrated in an external cohort. Through external validation, it would be possible to use relevant tests such as estimated calibration slope. Estimated calibration slope is less relevant with internal validation due to the average of predicted risks matching the event rate, this is shown on Appendix 1 where the estimated calibration slope of each bootstrapped dataset for the cohort is shown is equal to one. [155]

Another limitation to the study would be the inclusion of prior history of cancer as a predictor in the study. This is because prior history of cancer included patients who have undergone screening for cancer, which may have not resulted in an outright diagnosis. As a result, it cannot be reported that prior history of diagnosis of cancer is categorically not an independent predictor of mortality in heart failure patients.

5.2 Interpretation

The results display a range of findings describing the cohorts' features surrounding mortality within a 12-month period and the significance of predictors to that outcome. However, many of the hazard ratios associated with these predictors show counterintuitive results, which do not necessarily affect the validity of the model. Many of these predictors can trigger medical interventions, which we may not have added to the model. This relevant for predictors such as prior history of smoking and prior history of coronary heart disease for example.[156] In addition to this, the model performance was very good with an AUC of 0.79 after internal validation and a D-statistic of 1.6. A simple risk score based on splitting prediction scores into quartiles was able to show a statistically significant trend of mortality increasing with risk scores. This means that the model was able to discriminate between the outcomes of different patients well in this cohort.

5.2.1 Gender

This study had significantly more males who did not die during the period of follow up, and likewise males also had a lower mortality rate with Kaplan Meier curves also showing significantly higher survival for males. In the cox regression model females were 30% more likely to die within the follow up period when compared to males.

This result is in line with previous studies in the UK. A recent epidemiological study from Taylor et al in 2020 reported lower median survival for women but also reported a 14% lower mortality risk when compared to men. [157] The disparity in mortality risk between that study and this one could be explained by the fact that this study adjusted for much more predictors than just age. In addition to this, the study in question also had a much older population with a longer follow up period of 15 years. It could be the case that between a 1-year period, females had a higher mortality risk but over a 15-year period more females would have passed away compared to males leading to females having a much lower mortality risk, comparably. [157] In the United States of America, the 1-year hazard ratio for women compared to men in the Framingham Heart

Study was 0.64 (95% CI 0.54–0.77), indicating women were 36% less likely to die within a year after diagnosis. [42]

It must be noted that information on gender differences in heart failure outcomes is limited and not consistent. Many studies differ in their inclusion criterion and thus differences are explained through differences in baseline characteristics between their cohorts. In addition to this, many do not fully adjust their regression models and therefore the impact of confounding of other predictors is unknown. Without a fully adjusted multivariable model, it is difficult to compare these statistics by comparing mortality rate alone.

There is evidence to suggest that there are etiological differences between genders, such as female gender being associated with preserved left ventricular ejection fraction and male gender being associated with coronary arterial disease. [158] However, to fully understand these differences, their causes and how they may be managed, better gender data collection and research must be completed.

5.2.2 Age

Mean age was greater in the cohort that died during the follow up period compared to the cohort of patients that did not die during the follow up. Those who did not die were significantly younger in age group. Mortality rates also increased with age, with Kaplan Meier curves showing that there was a statistically significant trend of survival rates decreasing with age. In the multivariable prognostic model, there was a 6% increased risk of all-cause mortality within a year for every yearly increase in age at diagnosis.

The significance of age increasing risk in heart failure mortality is well documented in the literature and this study adds further evidence to that fact. A systematic review of risk prediction in patients with heart failure found age to be one of the most consistently reported predictors. [159] Many models have similar values for the increased risk however, differences exist which may be due to the difference in the predictors they have adjusted for. An example is the MAGGIC Model which estimates an increased risk of 15.4% per ten years

however this trial only adjusted for 13 independent predictors compared to the 29 in this study. [142]

5.2.3 Region

Data regarding region showed some important relationships. There was a significant difference between the regional make up of patients who did die during the follow up period and patients who did not die. Yorkshire and Humber had the highest mortality rate whilst the East Midlands had the lowest. There was a high degree of overlap between the 95% confidence intervals of several regions which calls into question the significance of the mortality rates. An example of this is Scotland and Wales which had confidence intervals of 12.91 to 13.94 and 12.91 to 14.09 respectively.

This is further supported by the fact that Kaplan Meier curves did not show a significant difference between the survival rates across regions and region was not found to be a significant predictor in the multivariable regression model.

Regional differences in HF mortality have not been well reported but this may be because of the lack of significant difference across regions.

5.2.4 Race

Race was poorly recorded in CRPD and did not provide any meaningful information in this analysis. Research also shows that race is not a valid biological category as there is more genetic variation within races than between races and that race is more of a social construct than a biological construct. [160] In addition to this there are issues with the validity and reliability of race in research studies as it is increasingly difficult to classify individuals into 1 racial category. An example of this in this study is the fact that a single person could be classed as “Mixed racial category”, “Afro-Caucasian racial category” or “Afro-Caribbean” category either through self-report or direct observation.

Another form of categorisation could be ethnicity. However, this leads to a similar issue. For example, a patient who elects to class themselves as Arab in ethnicity may be from either Iraq or Morocco, however these discrete

populations have heterogeneous genetic and epidemiological profiles despite identifying as the same ethnicity.

5.2.5 New York Heart Association Classification (NYHA)

NYHA classification was also poorly reported but to a lesser degree. Lower mortality rates were observed in NYHA classes 1-3, and higher rates of mortality in NYHA class 4. From mortality rate analysis it was clear mortality rates increased with classification and this was further demonstrated with the Kaplan Meier curves which showed that there was a significant trend in survival rate between different NYHA classes. NYHA was a significant predictor of mortality with risk increasing with class.

This data is in line with the literature. A 2014 systematic review found NYHA class to be one of the most significant and consistently reported predictors. [155] Like with previous predictors, whilst studies agree on increased risk with NYHA class, the individual values differ. An example of this is the MAGGIC score which indicates that an individual with an NYHA Class of 4 has a 68.4% increased risk of mortality over three years, ours indicate an 8 times increased risk of mortality over a year when compared to patients with an NYHA Class of 1 respectively. [142]

5.2.6 BMI Category

The study showed that patients with obesity classes I, II and III were significantly more represented within patients who did not die within the follow up period, whilst patients who were underweight and of normal weight were significantly more represented within patients who died within the follow up period Patients with obesity classes I, II and III also had the lowest mortality rates and underweight and normal weight patients having the highest mortality rate. This was again, further demonstrated by Kaplan Meier curves which also showed that there was a statistically significant trend in the association between survival rates and obesity class. In the multivariable cox- regression model however, once adjusted for all other significant predictors, risk seemed to increase with BMI, with underweight patients having a 37% reduced risk of mortality when compared to patients of normal weight and Obesity Class III

patients having around a 3 times increased risk of mortality when compared to patients of normal weight. Despite this there is a reduction in risk in Obesity Class I, but this is a smaller reduction than that of underweight patients.

This result is important because it indicates that the 'obesity paradox', [49] which describes the proposed protective effect of increased BMI on heart failure survival may be due to a lack of adjustment for the right set of confounders which may be responsible for the apparent protective effect. With this study controlling for the largest number of significant predictors to date in a risk model for heart failure survival, it would follow that the confounder responsible would be one of those directly or indirectly measured here.

5.2.7 Prior History of Atrial Fibrillation

This study showed that significantly more patients with atrial fibrillation died within the follow up period and that patients with atrial fibrillation had a higher mortality rate. Kaplan Meier also confirmed that patients with atrial fibrillation had a significantly lower survival rate however the multivariable regression model showed that once controlled for all other significant predictors, atrial fibrillation led to a 6% decrease in HF survival.

It may be the case that patients with prior history of AF were already receiving treatment that improves their mortality risk before being included in the cohort, treatments that have not been controlled for. This may support a study by chamberlain et all in 2011 which showed there to be an increased hazard risk for patients who were diagnosed with AF after being diagnosed with HF compared to the converse. [161]

5.2.8 Prior History of Alcohol Abuse

In multivariable analyses, alcohol abuse was found to increase the risk of mortality in patients with heart failure. Whilst there is evidence outlining the effects of alcohol consumption on developing heart failure [162] this study is one of, if not the first, outlining the effects of alcohol abuse on mortality in patients with Heart Failure.

5.2.9 Prior History of Anaemia

The study showed that patients with a prior history of anaemia also had a higher mortality rate than those who did not. The multivariable risk prediction model found anaemia to increase risk of mortality by 33%. Anaemia is a well-known and reported prognostic indicator for mortality in heart failure patients [163] and this study adds to the evidence to support this.

5.2.10 Prior History of Cardiomyopathy

Patients with cardiomyopathy also had a much lower mortality rate compared to those who did not, as shown by the Kaplan Meier Curves. However, a history of cardiomyopathy was not deemed to be a significant predictor of 1-year survival in the multivariable prediction model, this indicates that the significant differences in mortality rate were ultimately due to other factors that may have correlated with prior history of cardiomyopathy and not prior history of cardiomyopathy itself. Research on the effect of cardiomyopathy on HF mortality outcomes is limited and this study provides a useful addition.

5.2.11 Prior History of Cerebrovascular Disease

Significantly more patients who died during the follow up period had a history of cerebrovascular disease when compared to patients with who did not die. Despite this, patients with a prior history of cerebrovascular disease had a higher mortality rate. This was supported by Kaplan Meier curves which showed that these patients also had a significantly lower survival rate. However, after adjusting for the effect of confounders in the multivariable risk prediction model, cerebrovascular disease increased risk by 46%. This may mean that the mortality rates were likely due to confounders rather than to cerebrovascular disease itself.

Incident heart failure is known to be a risk factor for cerebrovascular disease such as stroke, death or both in the literature and this study adds to that evidence base. [164]

5.2.12 Prior History of Coronary Heart Disease

Patients with a prior history of coronary heart disease had a lower mortality rate than that of patients without a history of coronary heart disease and had a significantly higher survival rate as shown in the Kaplan-Meier curves. In an opposite fashion to that of cerebrovascular disease, the multivariable model found coronary heart disease to reduce risk by 10% when adjusted for all other confounders. Like cerebrovascular disease however, it seems the mortality and survival rates may have been because of confounders as opposed to coronary heart disease alone.

The significance of coronary heart disease on mortality outcomes for heart failure patients is well established in the literature [166] [165] However, many of these studies suggest an increase in risk from coronary heart disease whereas the model in this study suggests a decrease in risk. In this study, the decrease in risk may be because a diagnosis of coronary heart disease may have triggered intervention. In addition to this, many of these previous studies did not adjust for the number of confounders as this study has done and have had substantially smaller cohort sizes. Therefore, more research on large cohort sizes with adjustment for a comparable number of risk factors is necessary to establish the true link between coronary heart disease and HF mortality.

5.2.13 Prior History of Chronic Kidney Disease

A higher proportion of patients who died during the follow up period had a history of chronic kidney disease when compared to patients with chronic kidney disease who did not die. This was supported by the fact that patients with chronic kidney disease had a higher mortality rate than patients who did not and had a significantly lower survival rate in the Kaplan Meier curves. The multivariable model found prior history of chronic kidney disease to be significantly associated to the risk of 1-year mortality in heart failure patients. This is further examined in the creatinine and GFR sections of this discussion.

5.2.14 Prior History of Chronic Obstructive Pulmonary Disease

Significantly more patients who died during the follow up period had a history of chronic obstructive pulmonary disease when compared to patients with

chronic obstructive pulmonary disease who did not die. This was supported by the fact that patients with chronic obstructive pulmonary disease had a higher mortality rate than patients who did not and had a significantly lower survival rate in the Kaplan Meier curves. Prior history of COPD was not found to be significantly associated with 1-year mortality risk in heart failure patients.

5.2.15 Prior History of Cancer

In the multivariable model, Prior history of cancer was not found to be significantly associated with 1-year mortality in heart failure patients however this could be due to how cancer was defined in the study.

5.2.16 Prior History of Dyspnoea

Patients with a prior history of dyspnoea had a higher mortality rate than patients who did not and had a significantly lower survival rate as shown in the Kaplan-Meier curves. The multivariable risk model found prior history of dyspnoea to increase 1-year mortality risk in heart failure patients. This is one of the first studies to look at the mortality risk between concurrent dyspnoea and incident heart failure and provides a strong base for further research into this relationship.

5.2.17 Prior History of Hypercholesterolaemia

Patients with a prior history of hypercholesterolaemia had a lower mortality rate than patients who did not and had a significantly higher survival rate as shown in the Kaplan-Meier curves. In the multivariable regression model, prior history of hypercholesterolaemia was found to be significantly associated with increased mortality risk. This is further examined in the cholesterol section of this discussion.

5.2.18 Prior History of Hypertension

Prior history of hypertension was associated with a higher mortality rate and was further demonstrated by a significantly lower survival rate in the Kaplan-Meier curves. The multivariable model however found hypertension to increase risk in 1-year mortality in heart failure patients. A common topic in the literature is the paradoxical effect of high blood pressure being associated with

a reduction in mortality rates in HF patients.[167] In addition to this, a study by Tsimpoulis et al found that there was a 36% increase in mortality risk for patients with a systolic blood pressure less than 120 mmHg. These results are contrary to the risks reported in this study and this may be due to a range of factors. Further research must be completed to better understand the underlying reasons for these differences. [168]

5.2.19 Prior history of Left Ventricular Hypertrophy

Patients with a prior history of left ventricular hypertrophy had a lower mortality rate than that of patients who did not and had a significantly higher survival rate as shown in the Kaplan-Meier curves. Left ventricular hypertrophy was not found to be associated with 1-year mortality in heart failure patients. Whilst left ventricular hypertrophy is a well-known risk factor to develop heart failure [169] there is a limited number of studies that look at the mortality rates and survival rates of concurrent left ventricular hypertrophy and incident heart failure and this study provides a strong base for further research into this field.

5.2.20 Prior History of Pulmonary Congestion

Significantly more patients who did not die during the follow up period had history of pulmonary congestion when compared to patients with pulmonary congestion who did die. Despite this, patients with pulmonary congestion had a higher mortality rate that patients who did not – however there was not a significant difference in survival rates as per the Kaplan-Meier curves. The multivariable model found pulmonary congestion to increase the risk of 1-year mortality in HF patients. This is one of the first studies to look at the mortality risk between concurrent pulmonary congestion and incident heart failure and provides a strong base for further research into this relationship.

5.2.21 Prior History of Smoking

Patients with a prior history of smoking had a lower mortality rate than that of patients who did not and had a significantly higher survival rate as shown in the Kaplan-Meier curves. The multivariable model found prior history of smoking to reduce risk of mortality in 1-year for heart failure patients. This was a difficult result to interpret as the literature is otherwise clear about the beneficial

effects of smoking cessation on improving heart failure outcomes. A study by son et al in January 2020 found that persistent smoking after HF diagnosis increased risk of mortality and this would be expected. [170] It may be the case that in the cohort that most patients who had prior history of smoking went on to stop smoking, which is known to reduce mortality risk but is something that had had not measured or controlled for. Another case maybe that smoking may have triggered intervention which may have also reduced risk. Also, in terms of the way data is recorded and analysed, there may be a case mix as there isn't a sure way to discern between individuals who may have smoked in their youth and do not anymore, and individuals who currently smoke and have continued to smoke after being diagnosed with heart failure. Further research must be completed to assess the effect of smoking cessation on HF mortality risk.

5.2.22 Prior History of Type-2 Diabetes Mellitus

Patients with a prior history of type-2 diabetes mellitus had a higher mortality rate than that of patients who did not. Kaplan Meier curves however showed that there was not a significant difference in the survival rates for patients who had a prior history of type-2 diabetes and patients who did not. In the multivariable model, previous history of type-2 diabetes was found to significantly decrease risk of mortality in HF patients. This is one of the first studies to look at the effect of prior history of diabetes on mortality risk in HF patients. A 2019 American study which looked at a cohort of 86,669 heart failure patients with and without diabetes found diabetes to be independently and significantly associated with hospitalisations but not with mortality. This study adds to a literature base for further research on the topic. [171]

5.2.23 Prior History of ACE Inhibitor Use

Significantly more patients who did not die during the follow up period had previously used ACE inhibitors when compared to users of ACE inhibitors who died during the follow up period. Despite this, ACE inhibitors were found to increase risk of mortality in heart failure patients in the multivariable cox-regression model. This is a novel result considering that ACE inhibitors have been reported to reduce mortality in heart failure patients [168] [169] and have also

been an important part of national guidelines. Clinical trials which have been used to reference their efficacy such as the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and the SOLVD trial have methodological weaknesses when compared to this study. [174] [175] An example of this would be the fact that the CONSENSUS study reported statistically significant differences in crude mortality within treatment groups whilst the SOLVD trial excluded patients with renal impairment. Comparatively, this study uses multivariable logistic regression to establish mortality risk, which also adjusted for comorbidities such as chronic kidney disease and biomarker measurements such as creatinine concentration. As a result, the reported adjusted risk of mortality in this study has a stronger methodological base than that of the trials above. This result calls into question the use of ACE inhibitors in heart failure treatment and more research using multivariable methods need to be completed to better understand the relationship between ACE inhibitors and heart failure mortality.

5.2.24 Prior History of Beta-Blocker Use

Significantly more patients who did not die during the follow up period had previously used beta-blockers when compared to users of beta-blockers who died during the follow up period. The multivariable model found that beta blockers decrease 1-year all-cause mortality in heart failure patients. This is line with the literature which has long established the positive effects of beta blockers in reducing heart failure mortality. [176]

5.2.25 Prior History of Digoxin Use

Significantly more patents who died during the follow up period had previously used digoxin when compared to users of digoxin who did not die during the follow up period. In the multivariable model, digoxin was found to reduce 1-year mortality in HF patients. There is ongoing debate within the literature on the effect of digoxin on mortality in heart failure patients. Some studies assert that digoxin increases mortality, particularly in patients with atrial fibrillation [177] whilst other studies assert that it has no effect [178]. This study is one of the first to establish a reduction in mortality risk for patients with prior use of

digoxin before heart failure diagnosis and this may be due to the number of predictors adjusted for in the multivariable model. It may be the case that a number of these predictors, unmeasured, not controlled or not adjusted for in previous studies were otherwise responsible for the increased mortality risk.

5.2.26 Prior History of Diuretics Use

The multivariable model did not find diuretics to be a significant predictor of heart failure mortality. Diuretics are a have been a mainstay in heart failure treatment however there have been reports that they increase long term mortality and hospitalisation. [179] In addition to this, they are associated with side effects such as hypotension and hypokalaemia. [180] With the results of this study, there is added evidence supporting the non-routine need for their use with heart failure patients as they have a non-significant effect on mortality.

5.2.27 Prior History of Lipid Lowering Drug Use

Significantly more patients who did not die during the follow up period had previously used beta-blockers when compared to users of beta-blockers who died during the follow up period. Due to collinearity with statins, use of lipid lowering drugs was not included in further analyses.

5.2.28 Prior History of Statin Use

Significantly more patients who did not die during the follow up period had previously used statins when compared to users of statins who died during the follow up period. In the multivariable model statins were found to decrease risk by 54%, supporting the established effect of statins of HF mortality in the literature. [181 182]

5.2.29 Albumin Concentration

Mean albumin concentration was significantly higher in patients who did not die during follow up and was found to reduce risk for mortality in heart failure patients per unit increase. This is in line with evidence in the literature which establishes that hypoalbuminemia increases risk of mortality in heart failure patients. [183 184]

5.2.30 Bilirubin Concentration

Mean bilirubin concentration was significantly higher in patients who died during follow up and was found to slightly increased risk of mortality in heart failure patients per unit increase in concentration. Bilirubin is a well-known prognostic marker for heart failure mortality [185] and this study adds to the evidence base for this.

5.2.31 Systolic Blood Pressure

Mean systolic blood pressure was significantly higher in patients who died during follow up and was found to slightly increased risk for mortality for every unit increase. This is difficult to explain as hypertension increased risk by 21% and it may be the case that further stratification of blood pressure measurements may be necessary to ascertain the true effect between blood pressure and heart failure mortality.

In the literature, the 'paradoxical effect' of higher systolic blood pressure decreasing mortality in heart failure patients is well documented [167] [186] this study adds to that. However, like with the obesity paradox, it may be of value to stratify systolic blood pressure measurements in further research to better understand the relationship involved.

5.2.32 Cholesterol

Mean total cholesterol was significantly higher in the group of patients who did not die during follow up, however was not found to be a significant predictor in heart failure mortality. Mean HDL cholesterol was significantly higher in patients who died during follow up and was not found to be significantly associated with heart failure mortality in the multivariable model. Mean LDL cholesterol was significantly higher in patients who did not die during follow up and was found to significantly decrease risk per unit increase in the multivariable model. Mean VLDL cholesterol was significantly higher in the patients who died during follow up and was found to significantly increase risk per unit increase for mortality in HF patients.

Research looking at the effect of cholesterol in heart failure have been limited to total cholesterol (TC), with studies reporting lower serum cholesterol levels associated with a worse prognosis. [187] [188] This study is one of the first to look specifically at different subsets of cholesterol independently and to report that TC is not a significant predictor of HF mortality. In addition to this, the different risk profiles of LDL and VLDL may indicate that previous studies that showed lower serum cholesterol levels worsening prognosis may have included a larger proportion of patients with a higher VLDL to LDL ratio.

5.2.33 Creatinine

Mean creatinine was significantly higher in patients who died during follow up and was shown to increase risk per unit increase in the multivariable model. As creatinine is a biomarker used to measure kidney function, an increase in serum creatinine indicates a reduction in eGFR and kidney function. As increases in GFR was shown to decrease risk, it follows that increases in serum creatinine (assumed to be from a common baseline between patients) would also increase risk. This study is one of the first to epidemiologically look at the link between serum creatinine and HF mortality and provides an evidence base for further research into the topic.

5.2.34 C-Reactive Protein (CRP)

CRP was significantly higher in patients who died during follow up and was shown to increase risk per unit increase in the multivariable model. CRP is an established prognostic marker in heart failure [189] [190] and this study adds to the evidence available to support this.

5.2.35 Glomerular Filtration Rate (GFR)

Mean GFR was significantly higher patients who did not die during follow up and was found to be significantly associated with mortality, reducing risk slightly per unit increase in the multivariable model. This is an interesting result considering that previous history of chronic kidney disease also decreased risk in this study.

As the impact of low GFR and Kidney Disease on HF mortality is well established in the literature [191] this study asks an important question as to what confounders may be involved in this relationship and how they may play a role in this effect. It may also be valuable to stratify GFR and Kidney disease into different stages to better understand its true relationship with heart failure mortality.

5.2.36 Jugular Venous Pressure (JVP)

Mean JVP was significantly higher in patients who did not die during follow up and was found to be significantly associated with 1-year mortality in heart failure. Once adjusted for all other confounders JVP reduces risk by 6% for every unit increase. This is difficult to explain as studies have shown that elevated JVP increases mortality risk in HF patients and the measurement of JVP is used as a measure of right atrial function and central venous pressure. [16] More research is needed to ascertain the true effect on JVP on mortality risk and this may require stratifying JVP into discrete ranges as performed on BMI.

5.3 Comparison with other prognostic models

The prognostic model produced in this study can be compared to similar prognostic models produced previously.

5.3.1 Seattle Heart Failure Model (SHFM)

The Seattle Heart Failure Model was much smaller that the model produced in this study, with 22 predictors identified from a cohort of 1125 heart failure patients. This, compared to this study's model with 29 predictors from a cohort of over 109,000 patients is a much smaller model. As a result, this model has also demonstrated better accuracy with an AUC of 0.79, which is greater than that the majority of the AUCs of the SHFM's validation datasets (except for the University of Washington dataset which only had 148 patients). Predictors in the SHFM differed greatly to those in this model, an example of this is medications such as angiotensin receptor blockers, different types of diuretics and biochemical measurements such as uric acid, lymphocytes, and haemoglobin. Many of these were not included in the study as they were not well reported in CPRD. [136]

An important point to notes that this model has only been internally validated and the SHFM has been externally validated in several external cohorts. [137]

5.3.2 Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure (GISSI-HF)

The GISSI-HF prognostic model is similar to the model produced in this study as it was produced from a single country population (Italy) and has been internally validated on the cohort that it was built on. In comparison, this model is much smaller with only around 7000 patients compared to the 106,000 patients in this study. It is also significantly less accurate, with an AUC of 0.76 which is less than the 0.79 reported in this study. The GISSI-HF study looked at a significantly different set of predictors with 15 predictors in the final model not assessed in this study at all. This is because these predictors were not routinely recorded on CPRD. [181]

5.3.3 Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)

Whilst the MAGGIC model was built on a significantly larger dataset that both the SHFM model and the GISSI-HF model, it is still significantly smaller in size that the dataset used in this study and was also not formally validated or evaluated. Other than heart failure duration and ejection fraction, all of its final predictors for heart failure mortality were assessed in this study. [183]

5.3.4 Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM)

The CHARM model was built on the second largest cohort size with 7601 patients used to develop the prognostic model. Compared to the model produced in this study, the CHARM was highly selective with its inclusion criteria, with patients aged 18 or older who had symptomatic CHF of at least 4 weeks duration being eligible and those with serum creatinine ≥265 µmol/L, serum potassium ≥5.5 mmol/L, myocardial infarction or stroke in the prior 4 weeks, or non-cardiac disease judged to limit 2-year survival ineligible. In addition to this, the model found non-linear differences in risk between age and mortality as well as BMI and mortality – something untested in this study.

Finally, the model attained an AUC of 0.75 which was near to but still less than this study despite being much smaller and internally validated.[143]

5.4 Implication

5.4.1 Clinical implications

There are several possible clinical implications to this model, however it must be noted that these hazard ratios do not provide evidence of a causal link. Before further use in clinical practice the model would need to be externally validated in a range of different settings. This would ensure that the prognostic information delivered through its use remains accurate for patients using it. Once validated, the model would be useful for clinicians to better stratify the mortality risk level of their heart failure patients, which may lead to greater clinical efficiency and mortality reduction. An example of this would be to identify high risk groups for cardiac rehabilitation or to help triage patients for cardiologist referral.

A primary implication would be the increased use of prognostic modelling in the UK as this study has shown that this could be up 79% accurate, something which could improve patient clinician behaviour, help with patient targeting, patient surveillance, follow up and monitoring. [192 193]

The prescription of ACE inhibitors should be reviewed for heart failure, as this study has shown that they increase 1-year mortality risk. ACE inhibitors can be replaced of Angiotensin Receptor Blockers (ARB's) as indicated in the NICE guidelines. [103]

There is insufficient evidence to justify the inclusion (or role) of race in heart failure guidelines. This study found race to be poorly reported for observational research but is a clear part of national guidelines. As discussed in the discussion, race remains an invalid biological category and does not provide accurate genetic information. Current heart failure guidelines are stratified by the observed race of patients. [103 120 160]

Obesity remains an important risk factor for heart disease. Patients in obesity class II and III may be encouraged to lose weight as this would significantly reduce their mortality risk. Although the study shows further reductions in risk for patients as they become underweight, it is unclear whether this may have an adverse effect of their health, as this was not investigated in this study.

CRP, albumin, and bilirubin should be closely monitored in heart failure patients, in addition to systolic blood pressure, GFR and JVP.

As VLDL and LDL were found to be significant predictors, they should both be closely monitored in heart failure patients. Statins may be an essential part of heart failure therapy and guidelines due to their significant effect on mortality risk reduction.

5.4.2 Recommendations for future research

Further research must be linked studies that look at the full range of comorbidities, drugs and biomarkers implicated in heart failure. This is important as multivariable models, and the associated risk of a predictor can be significantly affected by the variables that have been adjusted for.

The effect of gender on mortality and the functional pathway for this effect must be examined. Further research should also consider the effect of interactions between age and gender and possible non-linear effects of BMI on mortality risk, as found in the CHARM study. [143]

The interaction of hypertension with heart failure mortality should be researched in detail in further studies as findings from this study were found to conflict with information in the literature. [168]

Further studies should explore the impact of smoking cessation on mortality risk as opposed to prior history of smoking alone.

The effects of ACE inhibitors must be further examined and if found to be associated with worse mortality outcomes, a functional pathway for this harm will be important to discover as it may open the door for better management.

This model must also be validated on an external dataset before being used for risk stratification in practice.

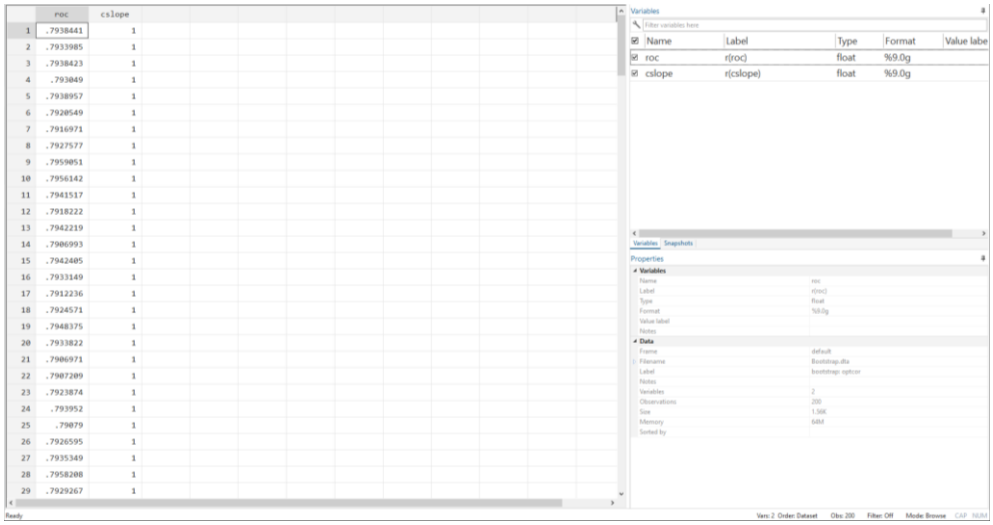
5.5 Conclusion

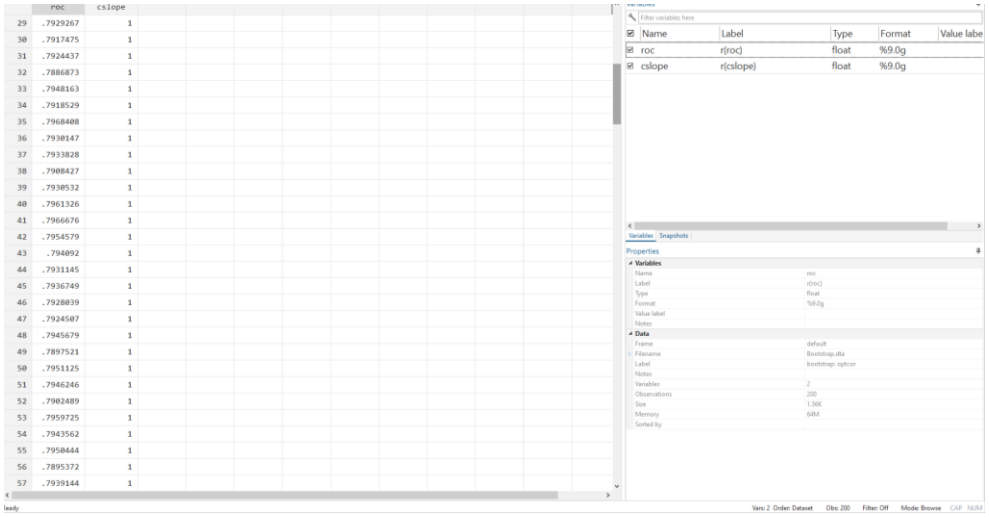
In conclusion, this study has successfully produced a prognostic model that predicts 1-year heart failure mortality through several significantly associated comorbidities, drugs, and biomarkers. This model has been internally validated to an AUC of 0.79 which showed excellent calibration. Through multivariable risk modelling and stratification, lower BMI has been found to decrease mortality risk, with an exception being Obesity Class I patients having a lower hazard risk ratio than Pre-Obesity patients. Further research must be completed to better understand the complete system of predictors and confounders responsible for HF mortality.

6 Other Information

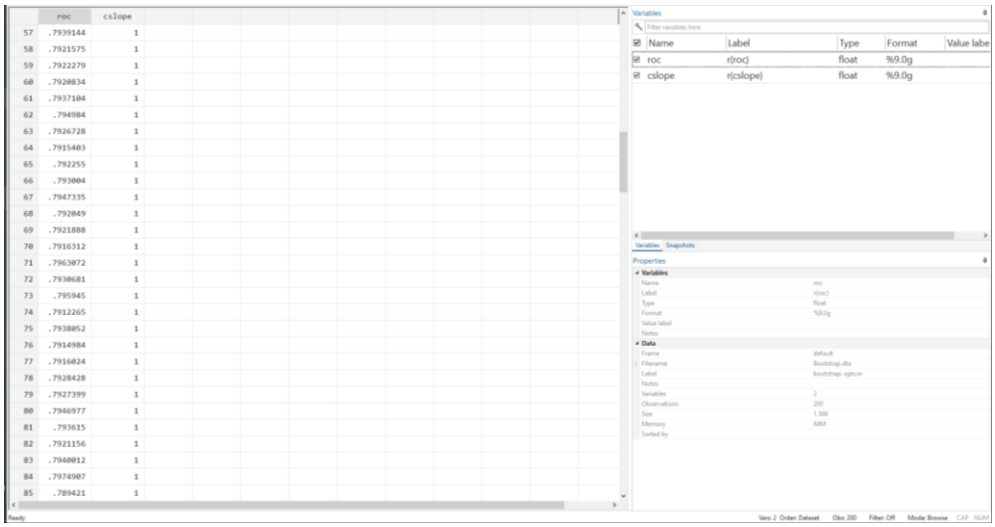
6.1 Supplementary Information

6.1.1 Appendix 1: Estimated Calibration Slope for Bootstrap Validation

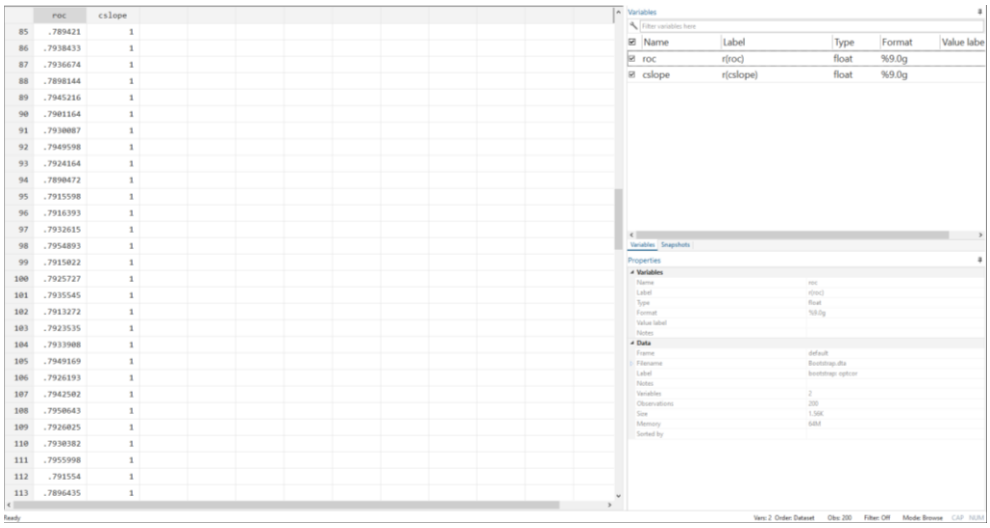




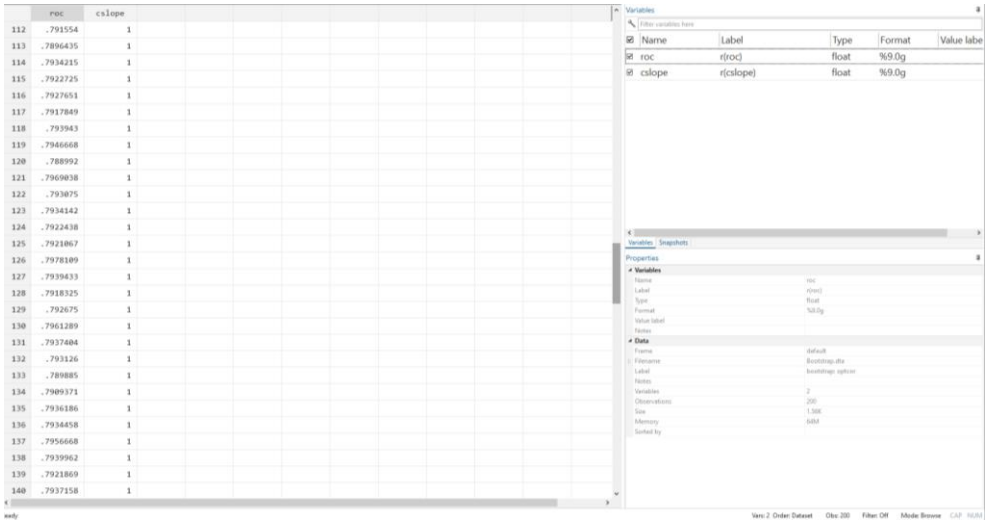
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35	.7968408	1
36	.7930147	1
37	.7933828	1
38	.7908427	1
39	.7930532	1
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45	.7936749	1
46	.7928039	1
47	.7924507	1
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49	.7897521	1
50	.7951125	1
51	.7946246	1
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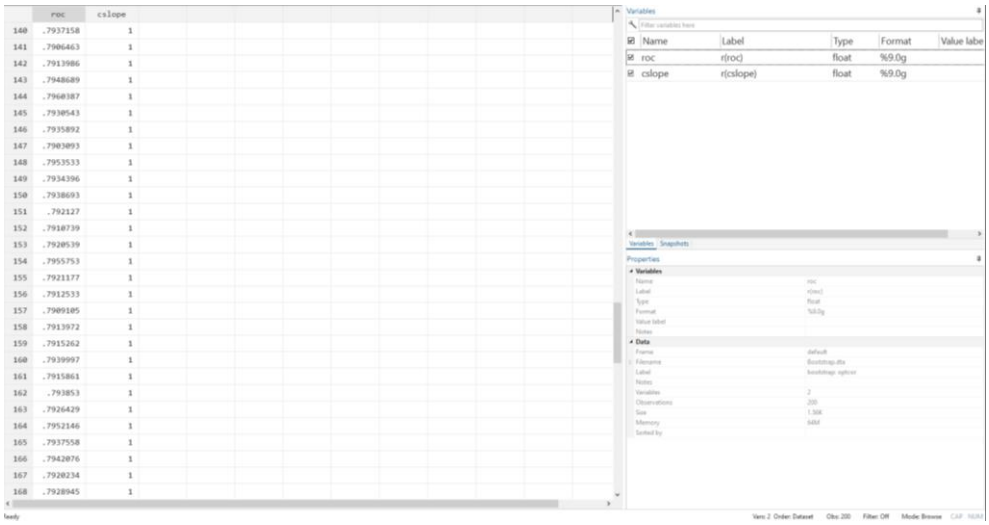
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79	.7927399	1
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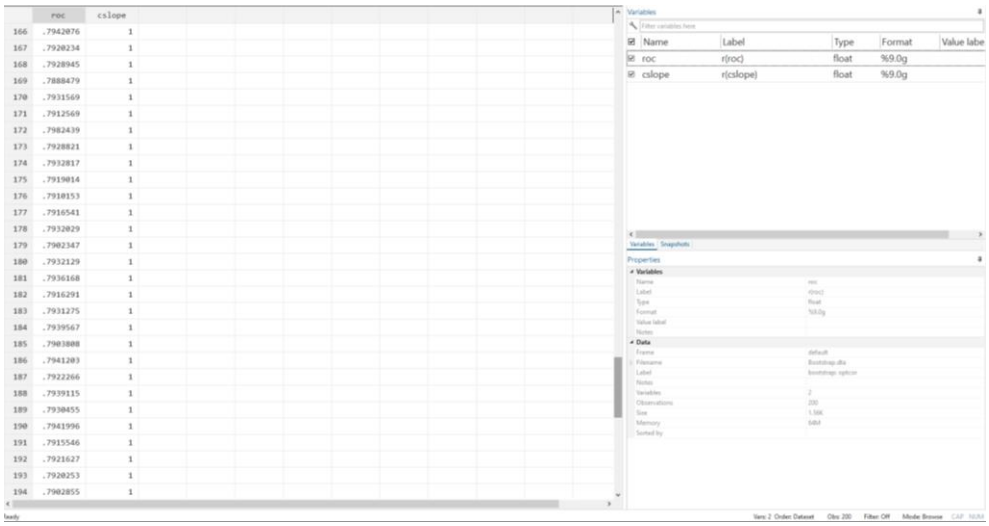
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102	.7913272	1
103	.7923535	1
104	.7933908	1
105	.7949169	1
106	.7926193	1
107	.7942502	1
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113	.7896435	1



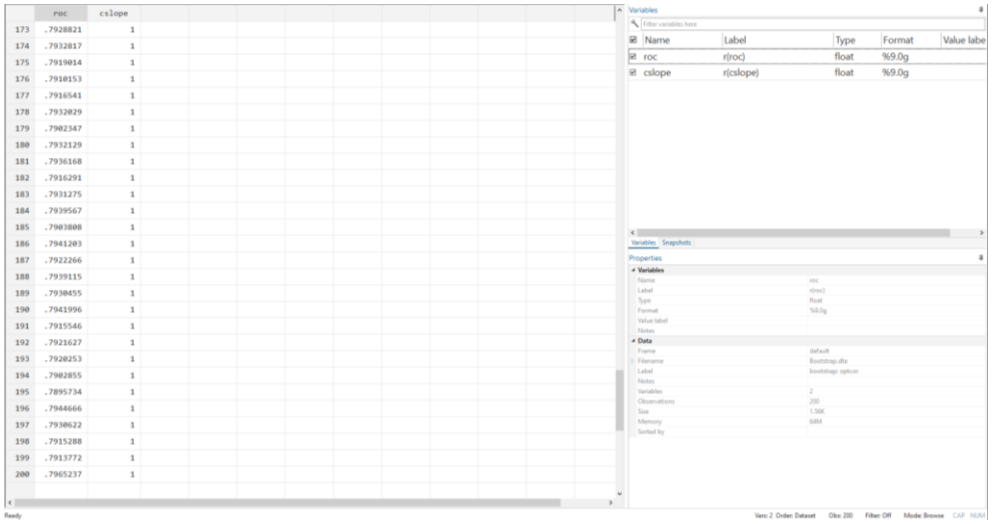
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118	.793943	1
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120	.788992	1
121	.7969038	1
122	.793075	1
123	.7934142	1
124	.7922438	1
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126	.7978109	1
127	.7939433	1
128	.7918325	1
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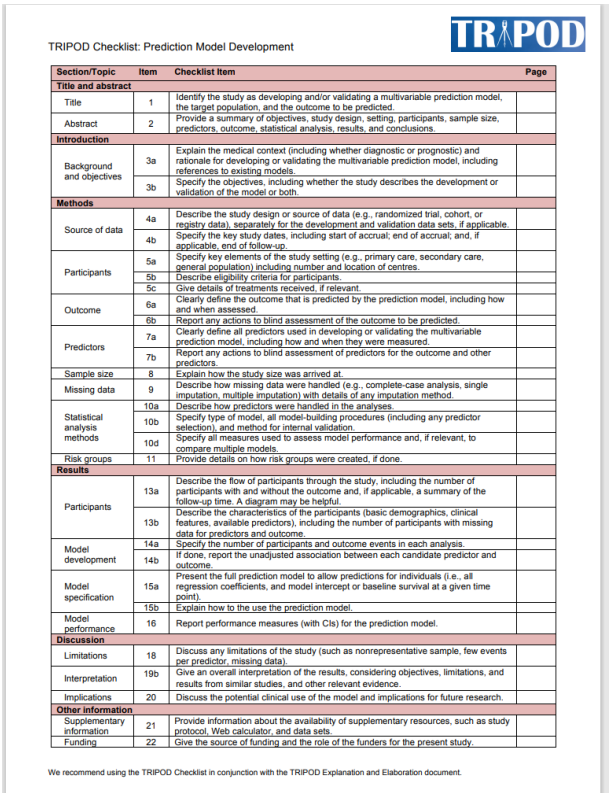


6.1.2 Appendix 2: Read Codes for Heart Failure

medcode	readcode	readterm
23707	G580000	Acute congestive heart failure
27964	G582.00	Acute heart failure
5255	G581000	Acute left ventricular failure
23481	G581.11	Asthma - cardiac
9524	G580.14	Biventricular failure
1223	G58..11	Cardiac failure
17278	G58z.12	Cardiac failure NOS
32671	G580100	Chronic congestive heart failure
11424	G580300	Compensated cardiac failure
2906	G580.11	Congestive cardiac failure
398	G580.00	Congestive heart failure
94870	G580400	Congestive heart failure due to valvular disease
27884	G580200	Decompensated cardiac failure
2062	G58..00	Heart failure
4024	G58z.00	Heart failure NOS
5942	G581.13	Impaired left ventricular function

12550	G5yyA00	Left ventricular diastolic dysfunction
884	G581.00	Left ventricular failure
8966	G5yy900	Left ventricular systolic dysfunction
18853	662f.00	New York Heart Association classification - class I
13189	662g.00	New York Heart Association classification - class II
19066	662h.00	New York Heart Association classification - class III
51214	662i.00	New York Heart Association classification - class IV
43618	G581.12	Pulmonary oedema - acute
22262	G1yz100	Rheumatic left ventricular failure
10079	G580.12	Right heart failure
10154	G580.13	Right ventricular failure
12590	G58z.11	Weak heart

6.1.3 Appendix 3: Tripod Checklist



TRIPOD Checklist: Prediction Model Development

TRIPOD

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	
	5b	Describe eligibility criteria for participants.	
	5c	Give details of treatments received, if relevant.	
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	
	6b	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	Explain how the study size was arrived at.	
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	
Risk groups	11	Provide details on how risk groups were created, if done.	
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	
Model development	14a	Specify the number of participants and outcome events in each analysis.	
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	
	15b	Explain how to the use the prediction model.	
Model performance	16	Report performance measures (with CIs) for the prediction model.	
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	
Implications	20	Discuss the potential clinical use of the model and implications for future research.	
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

6.2 Funding

This study was funded through the Aziz Foundations Master's Scholarship grant.

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